Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 03-112342

54 **TÍTULO** AGONISTAS DE DOPAMINA HIDROTOPICOS ADMINISTRADOS A LA PIEL

51 **CLASIFICACIÓN INTERNACIONAL** A61K 9/70

71 **SOLICITANTE** Pharmacia Corporation

DOMICILIO Chesterfield, Missouri 63017, Estados Unidos de America

74 **APODERADO** Tirado Mesa Duque

22 **BOGOTÁ, D C,** 24-12-2003

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PETITORIO

AS: 92.874

Industria y Comercio
SUPERINTENDENCIA

03 112342 00

SUPERINTENDENCIA Y EXPEDIENTE
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Presente : 011 PCT-ORIGEN 379 FASE NACI 411 PRESENTE
Dependencia: 2020 DIVISION DE NUEVAS SOLICITUDES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **PHARMACIA CORPORATION** Dirección: P.O. BOX 1027, Chesterfield, Missouri 63006, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número _____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: Thomas C. Pinkerton Dirección: 2400 Ridgeview Drive, Kalamazoo, MI 49008, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos de América	

5 PCT (86)
Solicitud Internacional No. PCT/US02/19918 Fecha 24-06-2002
Publicación Internacional No. WO 03/002103 A3 Fecha 09-01-2003

6 Título (54): AGONISTAS DE DOPAMINA HIDROFOBICOS ADMINISTRADOS A LA DERMIS

7 Clasificación Internacional (51) A61K 9/70

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	29-06-2001	09/897.801

9 Comprobante de pago No. 03-81472 **Fecha** 24-12-2003

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10 ANEXOS

2

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $400.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del Inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3

— SUPERINTENDENCIA Y COMERCIO
Radicacion : 03112642 00000000 Folios: 01
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FECHA : NOVIEMBRE 7 DE 2003

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	1374303	07/11/2003	15,620,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
		TOTAL : $	4 ,000.00

SON: CUATROCIENTOS MIL PESOS

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

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(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
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(71) Applicant *(for all designated States except US)*: PHARMACIA CORPORATION [US/US]; Corporate Patent Department, 800 North Lindbergh Blvd., Mail Zone One, St. Louis, MO 63167 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: PINKERTON, Thomas, C. [US/US]; 2400 Ridgeview Drive, Kalamazoo, MI 49008 (US).

(74) Agents: HOLLAND, Donald, R. et al.; Harness, Dickey & Pierce, P.L.C., 7700 Bonhomme, Suite 400, St. Louis, MO 63105 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
10 April 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/002103 A3

(54) Title: HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS

(57) Abstract: A method for systemic administration of a hydrophobic dopamine agonist to a mammal is disclosed. The method involves delivering the hydrophobic dopamine agonist to the dermis of the mammal whereby improved systemic absorption is obtained compared to absorption produced upon delivering the substance subcutaneously by bolus administration.

INTERNATIONAL SEARCH REPORT

Int pplication No
PCT/US 02/19918

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/158 A61M37/00 A61K9/70

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61M A61N

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 37882 A (ELAN PHARM INC) 31 May 2001 (2001-05-31) page 2, line 24 - line 25 page 7, line 13 - line 16 page 8, line 13 - line 17 -/-	1,5-15, 20,22, 23, 27-37, 42,44, 45, 49-59, 64,66, 70-80, 85,87, 91-101, 106

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2002	13/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/US 02/19918

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 13903 A (BOEHRINGER INGELHEIM PHARMA ;BRECHT HANS MICHAEL (DE)) 1 March 2001 (2001-03-01) page 4, paragraph 4 page 4, last paragraph -page 5, paragraph 2 page 4, last paragraph -page 6, paragraph 1; claims 1,11,12,25,26	1-16,20, 22-38, 42, 44-60, 64, 66-81, 85, 87-102, 106
A	US 5 997 501 A (KELLY JOHN GERARD ET AL) 7 December 1999 (1999-12-07) the whole document	1-107
A	WO 00 74763 A (GEORGIA TECH RES CORP) 14 December 2000 (2000-12-14) the whole document	1-106
A	BRESSOLLE F ET AL: "A Weibull distribution model for intradermal administration of ceftazidime." JOURNAL OF PHARMACEUTICAL SCIENCES. UNITED STATES NOV 1993, vol. 82, no. 11, November 1993 (1993-11), pages 1175-1178, XP002225051 ISSN: 0022-3549 cited in the application the whole document	1-106
P,X	WO 01 52854 A (BOEHRINGER INGELHEIM PHARMA ;BRECHT HANS MICHAEL (DE); JUNG BIRGIT) 26 July 2001 (2001-07-26) page 3, line 26 - line 36 page 4, line 23 - line 27 page 5, line 27 - line 33 page 6, line 4 - line 14	1,5-18, 20, 22-24, 27-40, 42,44, 49-62, 64,66, 70-83, 85,87, 91-104, 106

78

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 02/19918

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-107 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

8.9

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 5-23, 27-45, 49-66, 70-87, 91-107 relate to a compound, defined by reference to a desirable characteristic or property, namely a "hydrophobic dopamine agonist". The term "hydrophobic dopamine agonist" defines the active agent by its pharmacological effect. However, a compound canot be sufficiently characterised by its pharmacological effect as it is done by an expression like "hydrophobic dopamine agonist", because it is impossible to know which substances are encompassed in this expression.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in example 1, those mentioned in claims 2-4, 24-26, 46-48, 67-69 and 88-90, those mentioned in the description at page 12, line 12 - page 13, line 8, and the concept of a hydrophobic dopamine agonist.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 02/19918

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0137882	A	31-05-2001	AU	3440601 A	04-06-2001
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WO 0074763	A	14-12-2000	AU	5461300 A	28-12-2000
			EP	1187653 A2	20-03-2002
			WO	0074763 A2	14-12-2000
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			WO	0152854 A1	26-07-2001
			US	2001034320 A1	25-10-2001

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

(19) World Intellectual Property Organization
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(43) International Publication Date
9 January 2003 (09.01.2003)

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(10) International Publication Number
WO 03/002103 A2

(51) International Patent Classification[7]: A61K 9/70

(21) International Application Number: PCT/US02/19918

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(25) Filing Language: English

(26) Publication Language: English

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(71) Applicant *(for all designated States except US)*: PHARMACIA CORPORATION [US/US]; Corporate Patent Department, 800 North Lindbergh Blvd., Mail Zone One, St. Louis, MO 63167 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: PINKERTON, Thomas, C. [US/US]; 2400 Ridgeview Drive, Kalamazoo, MI 49008 (US).

(74) Agents: HOLLAND, Donald, R. et al.; Harness, Dickey & Pierce, P.L.C., 7700 Bonhomme, Suite 400, St. Louis, MO 63105 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/002103 A2

(54) Title: ENHANCED PARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS

(57) Abstract: A method for systemic administration of a hydrophobic dopamine agonist to a mammal is disclosed. The method involves delivering t he hydrophobic dopamine agonist to the dermis of the mammal whereby improved systemic absorption is obtained compared to absorption produced upon delivering the substance subcutaneously by bolus administration.

ENHANCED PHARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. application No. 09/897,801 filed June 29, 2001.

BACKGROUND OF THE INVENTION

(1) Field Of The Invention

[0002] The present invention relates to administration of substances into the dermis and, more particularly, to methods, compositions and devices for administration of hydrophobic substances into the dermis. Such administration results in systemic absorption, which is improved as compared to absorption obtained following subcutaneous administration.

(2) Description Of The Related Art

[0003] The importance of administering pharmaceutical substances such as diagnostic agents or drugs in a manner that results in good absorption and biologic effectiveness has long been recognized. Such biological effectiveness is dependent upon both systemic presentation of the substance as reflected in pharmacokinetic parameters and drug action as reflected in pharmacodynamic measurements (for review see Cawello et al, *J. Clin. Pharmacol. 37*:65S-69S, 1997; Wasan et al., *Arch. Med. Res. 24*:395-401 1993; Ratain, *Semin. Oncol. 19*:8-13, 1992).

[0004] Hydrophobic substances present a particular challenge in achieving desired biological effects due to difficulties in the preparation of delivery formulations coupled with the significant distribution of these substances into adipose tissue and storage in such tissue. (Steiner et al., *Drug Metab. Dispos. 19*:8-14, 1991; Xie et al, *Drug Metab. Dispos. 19*:15-19, 1991; Hough et al. *Life Sci. 58*:119-122, 1996). As a result, hydrophobic substances often show no more than limited systemic absorption following most conventional routes of administration. Commonly used routes for systemic administration have involved subcutaneous, intramuscular or intravenous delivery. All of these routes of administration can be considered transdermal administration, i.e. delivery

of substances through the skin to a site beneath the skin. Typically, conventional needles have been used for delivering substances transdermally although other approaches have also been used.

[0005] Anatomically, the outer surface of the body is made up of two major tissue layers, an outer epidermis and an underlying dermis, which together constitute the skin (for review, see *Physiology, Biochemistry, and Molecular Biology of the Skin, Second Edition*, L.A. Goldsmith, Ed., Oxford University Press, New York, 1991). The epidermis is subdivided into five layers or strata of a total thickness of between 75 and 150 μm. Beneath the epidermis lies the dermis, which contains two layers, an outermost portion referred to at the papillary dermis and a deeper layer referred to as the reticular dermis. The papillary dermis contains vast microcirculatory blood and lymphatic plexuses. In contrast, the reticular dermis is relatively acellular and avascular and made up of dense collagenous and elastic connective tissue. Beneath the epidermis and dermis is the subcutaneous tissue, also referred to as the hypodermis, which is composed of connective tissue and fatty tissue. Muscle tissue lies beneath the subcutaneous tissue.

[0006] As noted above, both the subcutaneous tissue and muscle tissue have been commonly used as sites for administration of pharmaceutical substances. The dermis, however, has rarely been targeted as a site for administration of substances, and this may be due, at least in part, to the difficulty of precise needle placement into the dermis. Furthermore, even though the dermis, in particular, the papillary dermis has been known to have a high degree of vascularity, it has not heretofore been appreciated that one could take advantage of this high degree of vascularity to obtain an improved absorption profile for hydrophobic substances compared to that achieved following subcutaneous administration. This is because small drug molecules are typically rapidly absorbed after administration into the subcutaneous tissue which has been far more easily and predictably targeted than the dermis has been. On the other hand, hydrophobic substances as well as large molecules such as proteins are typically not rapidly or entirely absorbed following subcutaneous administrations. Because hydrophobic substances tend to partition into subcutaneous adipose tissue the absorption of these substances into the vascular system would be expected to be limited following

subcutaneous administration (Walder, *Immunopharmacol. Immunotoxicol. 13*:101-119, 1991). Large proteins would also be expected to be slowly absorbed following subcutaneous administration and bioavailability has often been reported to be highly variable and incomplete (Porter et al., *Adv. Drug. Deliv. Rev. 50*:157-171, 2001). Furthermore, hydrophobic proteins can show poor absorption following subcutaneous administration measured by standard pharmacokinetic parameters, as compared to values obtained for proteins which are not hydrophobic. (see for example Thomsen et al., *Pharmacol. Toxicol. 74*:351-358, 1994). In spite of this, hydrophobic substances have not typically been administered into the dermis.

[0007] Numerous reports in the literature have reported on what has been described as "intradermal" administration. Such references, however, have often used the term "intradermal" according to its commonly used meaning of "intracutaneous", i.e. within the substance of the skin. This would including, primarily, subcutaneous tissue. In other references, so called "intradermal" placement of injected substances is intended to achieve no more than local administration of the substance and no attempt is made to achieve systemic bioavailability of the injected substances.

[0008] One such approach for achieving local administration of substances has been routinely used in the Mantoux tuberculin test. In this procedure, a purified protein derivative is injected at a shallow angle to the skin surface using a 27 or 30 gauge needle (Flynn et al, *Chest 106*: 1463-5, 1994). A degree of uncertainty in placement of the injection can, however, result in some false negative test results. Moreover, the test has involved a localized injection to elicit a response at the site of injection and the Mantoux approach has not led to the injection of substances into the dermis for the purpose of achieving systemic delivery of substances.

[0009] Similarly, local, "intradermal" injections of anesthetic drugs have been used to diminish the pain associated with i.v. catheter insertion and with suturing of lacerations (see for example Criswell et al., *Anaesthesia 46*:691-692, 1991; Anderson et al., *Ann. Emerg. Med. 19*:519-22, 1990). Such usage of local anesthetic drugs is, however, intended to be localized at the site of injection and systemic delivery of the local anesthetic agents is not obtained.

[0010] Some groups have reported on systemic administration by what has been characterized as "intradermal" injection. In one such report, a comparison study of subcutaneous and what was described as "intradermal" injection was performed (Autret et al, *Therapie 46*:5-8, 1991). The pharmaceutical substance tested was calcitonin, a protein of a molecular weight of about 3600, which is highly water soluble in the injectable form, was used. Similarly, Bressolle et al. administered the water soluble substance, sodium ceftazidime in what was characterized as "intradermal" injection(Bressolle et al. *J. Pharm. Sci. 82*:1175-1178, 1993). Neither of these studies provide any predictive information about absorption of hydrophobic substances following administration to the dermis.

[0011] Another group reported on what was described as an "intradermal" drug delivery device (U.S. Patent No. 5,997,501 to Gross et al.). Injection was indicated to be at a slow rate and the injection site was intended to be in some region below the epidermis, i.e., the interface between the epidermis and the dermis or the interior of the dermis or subcutaneous tissue. This reference taught administration with a particular device by infusion at slow rates which would not be expected show any improved systemic absorption as measured by pharmacokinetic parameters, compared that obtained following subcutaneous administration. This is because at slow infusion rates, the rate of infusion would be the rate limiting determinate of absorption and not tissue absorption barriers. As such, dermal absorption would not be expected to be greater than subcutaneous absorption.

[0012] Thus there remains a continuing need for effective methods and devices for administration of hydrophobic substances in a manner that achieves rapid and complete systemic absorption of the compounds.

SUMMARY OF THE INVENTION

[0013] Accordingly, the inventor herein has succeeded in discovering an approach for administration of hydrophobic substances in which improved absorption is achieved compared to that produced upon subcutaneous administration of the substances. The improved absorption is indicated by an improvement in at least one pharmacokinetic or pharmacodynamic parameter. The approach involves selectively delivering the

hydrophobic substances into the dermis. Delivery of the hydrophobic substance is to the dermis or into a region in close proximity to the dermis such that absorption takes place predominantly in the dermis. Preferably, the hydrophobic substance is administered by bolus, i.e. within a short period of time of about 10 minutes to about 15 minutes or less and, more preferably within 2 minutes or less. Surprisingly, such delivery to the dermis results in an improvement in pharmacokinetic and/or pharmacodynamic measurements as compared to what is produced upon subcutaneous administration.

[0014] Thus, the present invention provides, in one embodiment, a method for systemic administration of a substance to a mammal. Preferably, the mammal is a human although companion animals such as dogs and cats, farm animals such as pigs and cows, exotic animals such as zoo animals and the like are also included within the scope of the present invention.

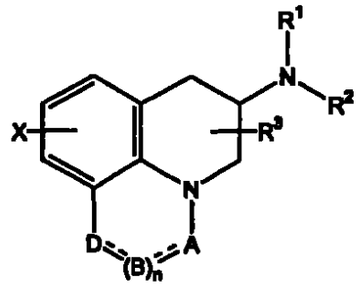
[0015] The term "hydrophobic" as used with respect to a substance administered into the dermis or subcutaneous tissue, is intended to mean that the substance tends to preferentially partition into lipophilic compartments such as can be found in subcutaneous adipose tissues rather than into aqueous extracellular fluids. The hydrophobicity of a substance can be assessed by standard methods such as, for example, by determining the oil-water distribution coefficient, preferably, the *n*-octanol/water distribution coefficient (see for example, Buchwald, *Curr Med Chem* 5:353-380, 1998). Values are typically expressed as the hydrophobicity or log value of partition coefficient, logP, under appropriate physiologic conditions. Such conditions will depend upon the conditions of the target region of administration in the mammal including temperature, pH, concentration and the like. Also, log of octanol-water partition coefficients can be estimated by using a variety of calculation programs, such as the one developed by Syracuse Research Corporation (Meylan and Howard, *J. Pharm. Sci. 84*: 83-92, 1995).

[0016] A threshold value of $\log P_{oct}$ which correlates with partitioning into adipose tissue is between 1.0 and 2.0 as has been shown by Steiner et al. for barbiturate compounds (Steiner et al., *Drug Metabolism and Disposition 19*:8-14, 1991; see, in particular, Fig. 4). This has also been shown for a number of basic drugs (Betschart et al, *Xenobiotica 18*:113-121, 1988; see, in particular, Fig. 2). Thus the hydrophobic

substances of the present invention have a threshold logP value greater than 1.00 preferably, at least about 1.5 or greater. A linear relationship has been shown between adipose tissue uptake and logP values up to 5 and greater for some compounds (Betschart et al., *supra*). Thus, in certain embodiments, it is desirable that the hydrophobic compound have a $logP_{oct}$ of greater than 1.5, i.e., at least about 2.0 or greater, at least about 2.5 or greater, at least about 3.0 or greater, at least about 3.5 or greater, at least about 4.0 or greater, or at least about 5.0 or greater.

[0017] The hydrophobic substances of the present invention can be small molecular drugs or diagnostic agents or large molecules such as proteins, polysaccharides or other polymeric compounds. The hydrophobic substances of the present invention include the non-limiting examples, anticonvulsant hydantoins, barbituric acids, HIV protease inhibitors, antiviral nucleosides, tricyclic nitrogen-containing compounds for central nervous system and sexual dysfunction conditions as well as numerous other hydrophobic substances. The invention is particularly applicable to tricyclic nitrogen-containing compounds useful in treating sexual dysfunction in men and women as disclosed in International Patent Publication No. WO 00/40226. Compounds of this class were earlier disclosed in U.S. Patent No. 5,273,975 (both WO 00/40226 and U.S. Patent No. 5,273,975 are incorporated in their entireties, by reference).

Such compounds are of the formula (I)



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl

groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

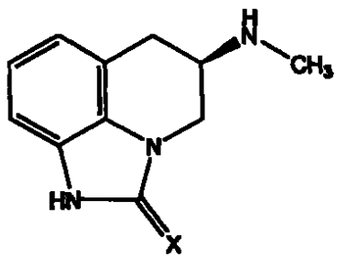
A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3;

with various provisos as indicated in WO 00/40226.

Preferred compounds useful in methods of the present invention are those disclosed generically or specifically in above-cited U.S. Patent No. 5,273,975. Especially preferred compounds are those of formula (II)



(II)

wherein X is O or S.

[0018] The improved systemic absorption produced by delivery to the dermis can be measured by any one of a number of standard pharmacokinetic and/or pharacodynamic parameters such as, for example, increase in bioavailability, decrease in T_{max}, increase in C_{max}, decrease in T_{lag}, or the like. By bioavailability is meant the total amount of a given dosage that reached the blood compartment. This is generally measured as the area under the curve in a plot of concentration vs. time, i.e. AUC. Although, bioavailability theoretically includes the total amount reaching the blood compartment over an infinite time period after dosage, as a practical matter, bioavailability is measured over a finite time interval of several hours after dosing, such as for example, about 2 hours, about 4, hours, about 6 hours, about 8, about 12 hours, about 14 hours or about 24 hours after dosing or longer.

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[0019] By "lag time" or T_{lag} is meant the delay between the administration of a compound and time to measurable or detectable blood or plasma levels. Although T_{lag} will be dependent upon the sensitivity of the assay method measuring or detecting the blood or plasma levels of a substance, the decrease in T_{lag} is independent of assay method because the same assay method is used to measure blood or plasma levels under the comparator conditions to show the decrease in T_{lag}. For example, the same assay system is used to compare plasma levels after subcutaneous administration and after administration of a substance to the dermis. A shorter time for achieving detectable levels of the substance, following administering into the dermis compared to subcutaneous administration, indicates improved absorption.

[0020] T_{max} is a value representing the time to achieve maximal blood concentration of the compound, and C_{max} is the maximum blood concentration reached with a given dose and administration method. The time for onset of action is related to T_{lag}, T_{max} and C_{max}, inasmuch as all of these parameters influence the time necessary to achieve a blood (or target tissue) concentration necessary to realize a biological effect. T_{max} and C_{max} can be determined by visual inspection of graphical results and can often provide sufficient information to compare two methods of administration of a compound. However, numerical values can be determined more precisely by analysis using kinetic models (as described below) and/or other means known to those of skill in the art.

[0021] Delivery into the dermis can be with any of a wide variety of devices which produce a cutaneous micropore such as is produced by any solid projection, electromotive force, thermal energy or gas ballistics. Such devices are referenced herein as poration devices, in particular microporation devices, or dermal-access devices. Preferably delivery is through one or more hollow needles although needleless or needle-free ballistic injection of fluids or powders into the ID space, iontophoresis, electroporation, or direct deposition of fluid, solids, or other dosing forms into the skin and the like are also within the scope of the present invention so long at least one cutaneous micropore is established by the delivery device.

[0022] The methods of the present invention can involve, in one embodiment, a selective delivery of the hydrophobic substance to the dermis. Such selective delivery

involves intentional placement of the substance in the dermis or in the region of the dermis which will or does result in access to and unimpeded absorption of the substance in the dermis as compared to placement in any other region of the skin. The selective delivery can comprise, in whole or in part, a recognition that delivery of the substance is to the dermis. In one aspect of this embodiment, the delivery of the substance to the dermis results in systemic absorption and, preferably, improved systemic absorption is obtained. Such improved systemic absorption can comprise a substantially higher bioavailability and/or a substantially higher C_{max}, and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag}. In a variation of the embodiment, the delivery is intended to achieve systemic absorption, and preferably, improved systemic absorption. Such selective delivery to obtain improved systemic absorption can comprise, in whole or in part, measurement of one or more pharmacokinetic parameters showing such improvement.

[0023] Among the several advantages achieved by the present invention, therefore, may be noted the provision of a new parenteral route of administration of hydrophobic substances which can achieve systemic delivery of the substances; the provision of a method of administration suitable for obtaining rapid onset of action of hydrophobic substances; the provision of methods suitable for obtaining repeated bolus administrations which mimic the pulsatile, rapid release of natural hormones; the provision of methods which allow intermittent and/or pulsatile administration of hydrophobic hormones or mimetics which avoids any receptor down regulation elicited by continuous blood levels of the hormones; the provision of a mode of administration which achieves a high absorption and bioavailability to allow less active drug to be used at a reduction in cost and a diminished likelihood of side effects; the provision of method of administration of a hydrophobic substance which can achieve higher blood levels than that achieved with subcutaneous administration of the same dose level; the provision of a method of administration which produces increases efficacy of the substance without altering systemic elimination rates and without altering pharmacodynamic effects; the provision of a method which avoids the substance being trapped in subcutaneous tissue lipophilic compartments to produce a depot effect; the provision of a method which is amenable to a regulated dose regimen as a result of rapid absorption of administered

substance; and the provision of a method of cutaneous administration which when implemented with a hollow needle device, places the substance directly in the dermis to avoid metabolic degredation and/or immunologic activity which can occur in the epidermis.

DETAILED DESCRIPTION OF THE INVENTION

[0024] In accordance with the present invention, it has been discovered that administration of a hydrophobic substance to the dermis results in improved systemic absorption of the substance.

[0025] The hydrophobic substances of the present invention tend to be of low water solubility or to be water insoluble, but soluble in non-polar solvents. Hydrophobicity of a substance can be assessed by standard methods such as, for example, by determining the oil-water distribution coefficient, preferably, the *n*-octanol/water distribution coefficient (see for example, Buchwald, *Curr Med Chem* 5:353-380, 1998). The oil-water distribution is the ratio of concentration of a compound in a water-immiscible non-polar solvent phase, such as *n*-octanol to the concentration in a water phase in contact with the solvent phase. Values are typically expressed as the log value of partition coefficient, logP, under appropriate physiologic conditions. Such conditions will depend upon the conditions of the target region of administration in the mammal including temperature, pH, concentration and the like.

[0026] For substances which are ionizable, the pK values or the negative log of the dissociation constant of such substances are a consideration and these values are sometimes determined at the same time that hydrophobicity is determined. This is because the partition coefficient is the ratio of concentration of a substance as the neutral molecule in a water-immiscible solvent to its concentration in an aqueous phase. Therefore, it is important to know the amount of neutral species present and this can be determined the pK of the substance and the pH of the aqueous solution. The pKa is the negative log of the equilibrium constant of an acid and the pKb is the negative log of the equilibrium constant of a base. As a practical matter, an acid having a pKa of one or more units greater than 7.4, i.e. 8.4 or greater, or a base having a pKb of one or more units less than 7.4, i.e. 6.4 or less are each predominantly in the form of the neutral

molecule at a physiologic pH of 7.4 and this neutral form will partition substantially into the oil phase in an oil-water distribution test.

[0027] Another factor which will influence the measured value of logP, in addition to pH, is the particular non-polar solvent used in the oil phase. Typically, *n*-octanol is the non-polar solvent because this substance has a carbon to oxygen ratio, which is similar to that of lipid material in animal fats. Thus, the *n*-octanol partition coefficient is believed to reflect the distribution of a substance administered to a subject into regions of the body containing a significant amount of adipose tissue.

[0028] The partition coefficient of a substance can be measured by any of a number of methods known in the art. These include, for illustrative purposes only, potentiometric methods such as with PCA101 of GlpKa(TM) devices (Sirius Analytical Instruments, Ltd, East Sussex, UK) which measure both pKa and partition coefficient, filter probe methods (Tomilinson, *J. Pharm. Sci 71*:602-604, 1982); reverse phase HPLC methods (see for example, Valko et al., *Curr. Med. Chem. 8*:1137-1146, 2001), flask shaking methods, predictive methods (see for example Buchwald et al., *Curr. Med. Chem. 5*:353-380, 1998) and the like.

[0029] The LogP has been shown to be related to aqueous solubility according to the following equation (Hansch et al., *J. Org. Chem. 33*:347-350, 1968):

$$\log S_w = -1.34 \log P_{oct} + 0.99$$

where $\log S_w$ is the molar solubility and $\log P_{oct}$ is the water-oil partition coefficient. Using this equation, values for $\log P_{oct}$ can be calculated from solubility data.

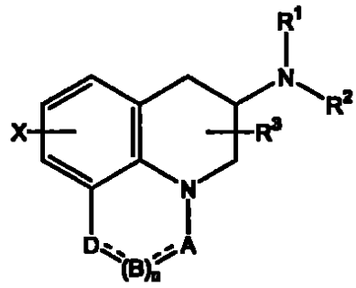
[0030] The hydrophobic substances of the present invention preferably show an *n*-octanol-water partition coefficient of at least about 1.5 or greater, more preferably at least about 2.0 or greater, and in certain embodiments, preferably at least about 2.5 or greater, at least about 3.0 or greater, at least about 3.5 or greater or at least about 4.0 or greater..

[0031] Hydrophobic substances that can be delivered into the dermis in accordance with the present invention are intended to include pharmaceutically or

biologically active substances including diagnostic agents, drugs, and other substances which provide therapeutic or health benefits such as for example nutraceuticals.

[0032] The hydrophobic substances of the present invention can be small molecular drugs or diagnostic agents or large molecules such as proteins, polysaccharides or other polymeric compounds. The hydrophobic substances of the present invention include the non-limiting examples, anticonvulsant hydantoins, barbituric acids, HIV protease inhibitors, antiviral nucleosides, cyclooxygenase inhibitors, tricyclic nitrogen-containing compounds for central nervous system and sexual dysfunction conditions as well as numerous other hydrophobic substances.

[0033] The invention is particularly applicable to tricyclic nitrogen-containing compounds of the formula (I)



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

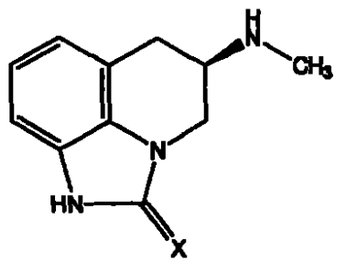
A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3;

with various provisos as indicated in WO 00/40226.

Especially preferred compounds are those of formula (II)



(II)

wherein X is O (sumanirole) or S (compound III) (see WO 00/40226 and U.S. Patent No. 5,273,975 which are incorporated in their entireties, by reference). Particularly preferred are compounds in the series useful for treatment of sexual dysfunction, especially, (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione and pharmaceutically acceptable salts as well as sumanirole which is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one and pharmaceutically acceptable salts.

[0034] Pharmaceutical acceptability refers to those properties which provide for suitability for administration to a subject including requirements of governmental agencies, patient acceptance and chemical and physical requirements which allow for manufacture, stability, bioavailability in a subject and the like. Pharmaceutically acceptable salts include salts of the following acids: maleic, methansulfonic, hydrochloric hydrobromic, sulfuric, phosphoric, nitric, benzoic, citric, tartaric, fumaric, and the like.

[0035] The LogP of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione was estimated to be 1.62 using logKow software (Syracuse Research Corporation, North Syracuse, NY 13212; see also Meylan and Howard, *supra*). In accordance with the present invention, this compound would be expected to produce higher C_{max} values and shorter T_{max} values upon administration to the dermis than that obtained following subcutaneous administration.

[0036] Additional hydrophobic substances within the scope of the present invention include the non-limiting examples of anticonvulsant hydantoins, barbituric acids, HIV protease inhibitors, cyclooxygenase inhibitors, antiviral nucleosides and pinene and its derivatives as shown in Table 1 below.

Table 1. LogP Values Of Hydrophobic Substances.

Compound	$LogS_w$ (moles/L)	$LogP_{oct}$*	Reference
ANTICONVULSANT HYDANTOINS			Stella et al, *J. Pharm. Sci,* 88:775-79, 1999
5,5-diphenyhlhydantoin	-4.10	3.80	
3-pentanoyloxymethyl-5,5-diphenylhydantoin	-4.68	4.23	
3-octanoloxymethyl-5,5-diphenylhydantoin	-6.52	5.60	
Anethole trithione	-5.80	5.07	
dithiolethione	-2.48	2.59	
5-phenyldithiolethione	-5.64	4.95	
dimethylthiolethione	-3.42	3.29	
BARBITURIC ACIDS			Prankerd et al*Int. J. Pharm.* 112:1-15,1994
5,5-dimethylbarbituric acid	-1.74	2.04	
5-Me-5-ethylbarbituric acid	-1.23	1.66	
5-Me-5-allylbartituric acid	-1.16	1.60	
5-Me-5-phenylbarbituric acid	-2.38	2.51	
5-Me-5-(3-methylbut-2-enyl)barbituric acid	-2.60	2.68	
5,5-diethylbarbituric acid	-1.40	1.78	
5-Et-5-iPr-barbituric acid	-2.15	2.34	
5-Et-5-allyl-barbituric acid	-1.61	1.64	
5-Et-5-phenyl-barbituric acid	-2.32	2.47	
5-Et-5-(3-methylbut-2-enyl)-barbituric acid	-2.25	2.42	
5,5-diphenylbarbituric acid	-4.20	3.87	
5,5-di-iPr-barbituric acid	-2.77	2.81	
5-iPr-5-allyl-barbituric acid	-1.71	2.01	
5-iPr-5-(3-methylbut-2-enyl)-barbituric acid	-2.59	2.67	

5-tBu-5-(3-methylbut-2-enyl)-barbituric acid	-3.55	3.39	
5-diallyl-barbituric acid	-2.08	2.29	
5-allyl-5-phenylbarbituric acid	-2.37	2.51	
5-diethyl-2-thiobarbituric acid	-2.17	2.36	
5-Et-5-(1-methylbutyl)-2-thiobarbituric acid	-3.68	3.49	
5,5-(CH2)2-barbituric acid	-1.89	2.15	
5,5-(CH2)3-barbituricacid	-1.66	1.98	
5,5-(CH2)4-barbituric acid	-2.35	3.97	
5,5-(CH2)5-barbituric acid	-3.06	3.02	
5,5-CH2)6-barbituric acid	-3.17	3.10	
5,5-(CH2)7-barbituric acid	-2.98	2.96	
5,5-(CH2)10-barbituric acid	-4.59	4.16	
5,5-(CH2)5-2-thiobarbituric acid	-3.46	3.32	
5,5-(CH2)11-barbituric acid	-5.80	5.07	
HIV PROTEASE INHIBITORS			Williams et al., *Adv. Drug Del. Rev.* 39:211-238, 1999
Didanosine	-0.90	1.48	
delavirdine	-4.76	4.29	
Efavirenz	-4.57	4.15	
Indinavir	-3.94	3.68	
Ritonavir	-5.16	4.52	
Amprenavir	-4.00	3.72	
Saquinavir	-4.33	3.97	
N-(3{(1R)-1-[(6R)-4-hydroxy-2-oxo-6-phenethyl-6-propyl-5,6-dihydro-2H-pyran-3-yl]propyl}phenyl)-5-(trifluoromethyl)-2-pyridinesulfonamide	-8.00*	6.71	log P estimated using SRC program (Meylan, et al. *J.Pharm. Sci. 84:* 83-92, 1995.)
ANTIVIRAL NUCLEOSIDES			Kristl, *Med.Res.*

N2-acetylacyclovir	-1.92	2.17	*Rev.* 7:417-440, 1999.
O-acetylacyclovir	-0.86	1.38	
N2,O-diacetylacyclovir	-2.70	2.75	

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PINENE AND DERIVATIVES			Fichan et al., *J. Chem. Eng. Data 44*:773-777, 1999
a-pinene	-3.66	3.47	
B-pinene	-3.91	3.66	
limonene	-3.41	3.28	
Myrcene	-3.58	3.41	
Borneol	-2.62	2.69	
fenchyl_alcohol	-2.27	2.43	
pinene_oxide	-2.59	2.67	
a-ionone	-3.06	3.02	
carveol	-1.88	2.14	
linalool	-2.00	2.23	
a-terpineol	-1.91	2.16	
Carvone	-1.67	1.99	
CYCLOOXYGENASE INHIBITORS			log P estimated using SRC program (Meylan, et al. *J.Pharm. Sci. 84:* 83-92, 1995.)
Celecoxib	-3.66*	3.47	
Valdecoxib	-2.59*	2.67	
Parecoxib	-3.16*	3.10	

*Log P_{oct} was calculated as $\log P_{oct} = (0.99 - \log S_w)/1.34$ except where otherwise indicated.

[0037] The pharmacokinetic profile for individual compounds will vary according to the chemical properties of the compounds. For example, compounds which are hydrophobic small molecules having a molecular weight of no more than 1000 Daltons are expected to show significant changes compared to traditional parenteral methods of administration, such as intramuscular, subcutaneous or subdermal injection. Furthermore, compounds which are hydrophobic and relatively large, having a molecular weight of at least 1000 Daltons as well as larger compounds of at least 2000 Daltons, at least 4000 Daltons, at least 10,000 Daltons and larger are expected to show the most significant changes compared to traditional parenteral methods of administration, such as intramuscular, subcutaneous or subdermal injection.

[0038] The enhanced absorption profile is believed to be particularly evident for substances which are not well absorbed when injected subcutaneously such as, for example, hydrophobic substances and, in particular, hydrophobic macromolecules. Macromolecules and, in particular, hydrophobic macromolecules are, in general, not well absorbed subcutaneously and this may be due, not only to their size relative to the capillary pore size, it may also be due to their slow diffusion through the interstitium because of their size and hydrophobicity. It is to be understood that hydrophobic macromolecules can possess discrete hydrophobic domains. In contrast, small molecules which are hydrophilic are generally well absorbed when administered subcutaneously and it is possible that no enhanced absorption profile would be seen upon injection into the dermis compared to absorption following subcutaneous administration.

[0039] The hydrophobic substances within the scope of the present invention can include conjugates which are covalently linked. Such conjugates can include the non-limiting examples of high or low molecular weight molecules conjugated with polyethylene glycol (PEG) and other polymers (for review, see Veronese, *Biomaterials 22*:405-417, 2001). Covalent attachment of PEG to a protein can greatly increase the protein half-life in blood. Protein-protein conjugates, i.e. fusion proteins, are also included within the scope of the present invention such as, for example, single-chain Fv (sFv) conjugates with effector proteins (for review, see Huston et al, *Int. Rev. Immunol 10*:195-217, 1993). Single-chain Fv antibodies can also be conjugated with small

molecules such as imaging tags (see for example, Begen et al, *Nat. Med.* 2:979-984, 1996) and such conjugates are also within the scope of the present invention.

[0040] By "improved pharmacokinetics" it is meant that an enhancement of pharmacokinetic profile is achieved as measured, for example, by standard pharmacokinetic parameters such as time to maximal plasma concentration (T_{max}), the magnitude of maximal plasma concentration (C_{max}) or the time to elicit a minimally detectable blood or plasma concentration (T_{ng}). By enhanced absorption profile, it is meant that absorption is improved or greater as measured by such pharmacokinetic parameters. The measurement of pharmacokinetic parameters and determination of minimally effective concentrations are routinely performed in the art. Values obtained are deemed to be enhanced by comparison with a standard route of administration such as, for example, subcutaneous administration or intramuscular administration. In such comparisons, it is preferable, although not necessarily essential, that administration into the dermis and administration into the reference site such as subcutaneous tissue, involve the same dose levels, i.e. the same amount and concentration of drug as well as the same carrier vehicle. Administration to the reference site can be at a bolus rate of administration method and/or administration can be at the at the same rate as administration to the dermis whether at a bolus rate of administration or at a slower, infusion rate of administration. Administration to the reference site at a bolus rate of administration is preferred for achieving a comparative enhancement of systemic absorption inasmuch as such bolus administration of hydrophobic substances to the subcutaneous tissue shows a diminished rate of systemic absorption compared to absorption of substances which are hydrophilic or substances which are less hydrophobic than the test substance (see for example, Fuji et al, *Exp. Anim.* 48:241-246, 1999). Thus, the improvement in systemic absorption as reflected in pharmacokinetic parameters is more pronounced following administration to the dermis as compared to values measured following bolus subcutaneous administration .

[0041] Comparison can also be at the same rate of administration in terms of amount and volume per unit time. Thus, for example, administration of a given pharmaceutical substance into the dermis at a concentration such as 100 µg/ml and rate of 100 µL per minute over a period of 5 minutes would, preferably, be compared to

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administration of the same pharmaceutical substance into the subcutaneous space at the same concentration of 100 μg/ml and rate of 100 μL per minute over a period of 5 minutes.

[0042] Administration of a hydrophobic substance to the dermis is intended to mean that the substances is placed in such a manner that the substance readily reaches the richly vascularized papillary dermis and is rapidly absorbed into the blood capillaries and/or lymphatic vessels to become systemically bioavailable. Such can result from placement of the substance in the upper region of the dermis, i.e. the papillary dermis or in the upper portion of the relatively less vascular reticular dermis such that the substance readily diffuses into the papillary dermis.

[0043] Mammalian skin contains two layers, as discussed above, specifically, the epidermis and dermis. The epidermis is made up of five layers, the stratum corneum, the stratum lucidum, the stratum granulosum, the stratum spinosum and the stratum germinativum and the dermis is made up of two layers, the upper papillary dermis and the deeper reticular dermis. The thickness of the dermis and epidermis in humans varies from individual to individual, and within an individual, at different locations on the body. For example, it has been reported that the epidermis varies in thickness from about 40 to about 90 μm and the dermis varies in thickness ranging from just below the epidermis to a depth of from less than 1 mm in some regions of the body to just under 2 to about 4 mm in other regions of the body depending upon the particular study report (Hwang et al., *Ann Plastic Surg 46*:327-331, 2001; Southwood, *Plast. Reconstr. Surg 15*:423-429, 1955; Rushmer et al., *Science 154*:343-348, 1966). The invention herein with respect to administration to humans, encompasses delivery of substances to the dermis at any desired location on the body. Thus the depth of placement of the substance will depend upon the depth of the dermis at the desired location. Such placement may be, for example, from up to about 1 mm in certain instances for abdominal skin (Hwang et al., *supra*) or up to about 4 mm in certain instances for skin of the back (Rushmer et al., *supra*).

[0044] For most areas of human skin, it is preferred that a substance be placed predominately at a depth of at least about 0.3 mm, more preferably, at least about 0.4 mm

and most preferably at least about 0.5 mm up to a depth of no more than about 2.5 mm, more preferably, no more than about 2.0 mm and most preferably no more than about 1.7 mm will result in rapid absorption of macromolecular and/or hydrophobic substances. Placement of the substance predominately at greater depths and/or into the lower portion of the reticular dermis is believed to result in the substance being slowly absorbed in the less vascular reticular dermis or in the subcutaneous region either of which would result in reduced absorption of macromolecular and/or hydrophobic substances. The controlled delivery of a substance to the dermis below the papillary dermis in the reticular dermis, but sufficiently above the interface between the dermis and the subcutaneous tissue, should enable an efficient (outward) migration of the substance to the (undisturbed) vascular and lymphatic microcapillary bed (in the papillary dermis), where it can be absorbed into systemic circulation via these microcapillaries without being sequestered in transit by any other cutaneous tissue compartment.

[0045] The present invention provides a method for therapeutic treatment by delivery of a hydrophobic drug or other substance to a human or non-human animal subject by directly targeting the dermis, wherein the drug or substance is administered through any one of a variety of dermal-access devices. Substances administered according to the methods of the invention have been found to exhibit improved pharmacokinetic parameters, and more clinically desirable than that observed for the same substance administered by subcutaneous injection, i.e. by bolus subcutaneous administration.

[0046] The microporation device or dermal-access device used for administration to the dermis according to the invention is not critical as long as it penetrates the skin of a subject to the desired targeted depth to the dermis without passing through the dermis to the subcutaneous tissue. In most cases, the device will penetrate the skin and to a depth of about 0.5-2 mm. The dermal-access means may comprise conventional injection needles, catheters or microneedles of all known types, employed singularly or in multiple needle arrays. The dermal-access means may comprise needleless devices including ballistic injection devices. The terms "needle" and "needles" as used herein are intended to encompass all such needle-like structures The term microneedles as used herein are intended to encompass structures smaller than about 30 gauge, typically about 31-50

gauge when such structures are cylindrical in nature. Non-cylindrical structures encompass by the term microneedles would therefore be of comparable diameter and include pyramidal, rectangular, octagonal, wedged, and other geometrical shapes.

[0047] Microporation or dermal-access devices also include ballistic fluid injection devices, powder-jet delivery devices, piezoelectric, electromotive, electromagnetic assisted delivery devices, gas-assisted delivery devices, of which directly penetrate the skin to provide access for delivery or directly deliver substances to the targeted location within the dermal space. The targeted depth of delivery of substances by the dermal-access means may be controlled manually by the practitioner, or with or without the assistance of indicator means to indicate when the desired depth is reached. Preferably however, the device has structural means for controlling skin penetration to the desired depth within the dermis. This is most typically accomplished by means of a widened area or hub associated with the shaft of the dermal-access means that may take the form of a backing structure or platform to which the needles are attached. The length of microneedles as dermal-access means are, preferably, less than 2 mm length. They may be used in the invention as individual single microneedles or in an assembly of multiple microneedles in linear or two-dimensional arrays so as to increase the rate of delivery or the amount of substance delivered in a given period of time. Microneedles may be incorporated into a variety of devices such as holders and housings that may also serve to limit the depth of penetration. The dermal-access devices of the invention may also incorporate reservoirs to contain the substance prior to delivery or pumps or other means for delivering the drug or other substance under pressure. Alternatively, the device housing the dermal-access devices may be linked externally to such additional components.

[0048] Microneedles suitable for administration to the dermis may, for example, have the dimensions of about 250 micron outer diameter, and less than 2 mm exposed length. The microneedles can be constructed of steel, other metals such as copper, nickel, titanium or mixtures thereof, silicon, ceramic, plastic, or any suitable material or combinations thereof.

[0049] The intravenous-like pharmacokinetics are achieved by administering a substance to the dermis in intimate contact with the capillary microvasculature and lymphatic microvasculature of the papillary dermis. In should be understood that the terms microcapillaries or capillary beds of the dermis are intended to refer to either vascular or lymphatic drainage pathways within the dermis.

[0050] While not intending to be bound by any theoretical mechanism of action, it is believed that the rapid absorption observed upon administration into the dermis is achieved as a result of the rich plexuses of blood and lymphatic vessels in the dermis. However, the presence of blood and lymphatic plexuses in the dermis would not by itself be expected to produce an enhanced absorption of hydrophobic substances because the substances tend to partition into lipophilic compartments in a depot fashion to thereby diminish their availability for absorption. The enhanced absorption observed upon administration of a hydrophobic substance to the dermis may, however, result from the lack of fat cells and, hence, the substantial absence of lipophilic compartments in the dermis. Another possible contribution to the unexpected enhanced absorption achieved upon delivery of hydrophobic substances to the dermis may result from an increase in blood flow and capillary permeability caused by injection into the dermis. For example, it is known that a pinprick insertion to a depth of 3 mm produces an increase in blood flow and this has been postulated to be independent of pain stimulus and due to tissue release of histamine (Arildsson et al., *Microvascular Res. 59*:122-130, 2000). This is also consistent with the observation that an acute inflammatory response elicited in response to skin injury produces a transient increase in blood flow and capillary permeability (see *Physiology, Biochemistry, and Molecular Biology of the Skin, Second Edition*, L.A. Goldsmith, Ed., Oxford Univ. Press, New York, 1991, p. 1060; Wilhem, *Rev. Can. Biol. 30*:153-172, 1971). At the same time, the injection into the dermis would be expected to increase interstitial pressure. It is known that increasing interstitial pressure from values from a normal value of about –7 mmHg to about +2 mmHg distends lymphatic vessels and increases lymph flow (Skobe et al., *J. Investig. Dermatol. Symp. Proc. 5*:14-19, 2000). Thus, the increased interstitial pressure elicited by injection into the dermis is believed to elicit increased lymph flow and increased absorption of substances injected into the dermis.

[0051] The administration methods useful for carrying out the invention include both bolus and infusion delivery of drugs and other substances to humans or animals subjects. A bolus dose is a single dose delivered in a single volume unit over a relatively brief period of time, typically about 10 minutes or less, more preferably about 2 minutes or less. Administration by bolus administration can be by a device suitable for accessing the dermis which also contains a mechanism for propelling the substance into the dermis such as, for example, a needle or microneedle coupled to a syringe driven by a pump. Alternatively, the syringe and needle delivery can be used manually by push while monitoring the injection time, typically about 2 minutes or less, with the second hand of a clock or watch.

[0052] Infusion administration comprises administering a fluid at a selected rate that may be constant or variable, over a relatively more extended time period, typically greater than about 10 minutes. To deliver a substance the dermal-access device is placed adjacent to the skin of a subject providing directly targeted access within the dermis and the substance or substances are delivered or administered into the dermis where they can act locally or be absorbed into the bloodstream and be distributed systematically. The dermal-access device may be connected to a reservoir containing the substance or substances to be delivered. Delivery from the reservoir into the dermis may occur either passively, without application of the external pressure or other driving means to the substance or substances to be delivered, and/or actively, with the application of pressure or other driving method. Examples of preferred pressure generating devices include pumps, syringes, elastomer membranes, gas pressure, piezoelectric, electromotive, elecrtomagnetic pumping, or Belleville springs or washers or combinations thereof. If desired, the rate of delivery of the substance may be variably controlled by the pressure-generating means. As a result, the substance enters the dermis and is absorbed in an amount and at a rate sufficient to produce a clinically efficacious result. Clinically efficacious results, as referenced herein, are intended to include both diagnostically and therapeutically useful responses, resulting from administration of a substance or substances.

[0053] The hydrophobic substances of the present invention are in a formulation suitable for administration to the dermis. The hydrophobic substance can be in the form

of a solution in a non-aqueous vehicle or a vehicle which is a mixture of water and a co-solvent. Non-aqueous vehicles and/or cosolvents include sugars and high molecular weight hydrophylic polymers (see for example, Yalkowsky, *Solubility and Solubilization in Aqueous Media*, Oxford University Press, New York, 1999). Non-limiting examples of such cosolvents include ethanol, propylene glycol, glycerin, sorbitol, polyethylene glycol 400, polyethylene glycol 4000, poloxamer 188, propylene carbonate, polyvinylpyrrolidone, dimethylisosorbide, *N*-methylpyrrolidone and combinations thereof. Among such formulations, the carrier vehicle for the hydrophobic substance will contain at least one cosolvent at a concentration of from about 5% to about 95% on a weight/weight basis. Preferred formulations will contain at least one cosolvent at a concentration of at least about 10%, at least about 20%, at least about 30%, at least about 40% up to about 50% or greater in an aqueous medium, on a weight/weight basis. Mixtures of cosolvents can also be used.

[0054] Surface active agents, i.e. surfactants, can also be present in the formulation as solubilizing agents. Such surfactants can be anionic, cationic, zwitterionic or nonionic (See for example, Yalkowisky, *supra*, pp. 236-320). Non-limiting examples of suitable surfactants include phospholipids such as lecithin, benzalkonium chloride, benzethonium chloride, cetylpyridinium chloride, dioctyl sodium sulfosuccinate, nonoxynol 9, nonoxynol 10, octoxynol 9, poloxamers, polyoxyethylene (8), caprylic/capric mono- and diglycerides (*e.g.*, Labrasol™ of Gattefossé), polyoxyethylene (35) castor oil, polyoxyethylene (20) cetostearyl ether, polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (10) oleyl ether, polyoxyethylene (40) stearate, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 (*e.g.*, Tween™ 80 of ICI), propylene glycol laurate (*e.g.*, Lauroglycol™ of Gattefossé), sodium lauryl sulfate, sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, tyloxapol, and mixtures thereof.

[0055] Formulations containing surfactants comprise, preferably, from about 1% or less up to about 15% surfactant on a weight/weight basis. Preferred surfactant concentrations are at least about 2%, at least about 3%, at least about 4%, up to about 5% on a weight/weight basis.

[0056] The hydrophobic substance can also be in the form of nanoparticles or nanocrystals dispersed or suspended in an aqueous medium. In such a formulation the hydrophobic substance is nanoparticulate, *i.e.*, having D_{90} less than about 1μm (D_{90} being a diameter such that 90% by weight of the particles are smaller than this diameter in their longest dimension). In such nanoparticulate formulations, weight average particle size is typically about 100 nm to about 800 nm, for example about 150 nm to about 600 nm, or about 200 nm to about 400 nm. The nanoparticles can also have a D_{25} particle size of about 450 nm to about 1000 nm, and more preferably about 500 nm to about 900 nm (D_{25} being a diameter such that 25% by weight of the particles are smaller than this diameter in their longest dimension). Pharmaceutical compositions comprising any of such nanoparticulate formulations of the hydrophobic substance can be useful in methods of the present invention.

[0057] Numerous processes for preparation of nanoparticulate compositions of therapeutic agents are known. Some of these processes use mechanical means, such as milling, to reduce particle size to a nano range, and others precipitate nano-sized particles from solution. Illustrative processes are disclosed in the patent publications cited below.

U.S. Patent No. 4,826,689 to Violanto & Fischer.
U.S. Patent No. 5,145,684 to Liversidge *et al.*
U.S. Patent No. 5,298,262 to Na & Rajagopalan.
U.S. Patent No. 5,302,401 to Liversidge *et al.*
U.S. Patent No. 5,336,507 to Na & Rajagopalan.
U.S. Patent No. 5,340,564 to Illig & Sarpotdar.
U.S. Patent No. 5,346,702 to Na & Rajagopalan.
U.S. Patent No. 5,352,459 to Hollister *et al.*
U.S. Patent No. 5,354,560 to Lovrecich.
U.S. Patent No. 5,384,124 to Courteille *et al.*
U.S. Patent No. 5,429,824 to June.
U.S. Patent No. 5,503,723 to Ruddy *et al.*
U.S. Patent No. 5,510,118 to Bosch *et al.*
U.S. Patent No. 5,518,187 to Bruno *et al.*
U.S. Patent No. 5,518,738 to Eickhoff *et al.*

U.S. Patent No. 5,534,270 to De Castro.
U.S. Patent No. 5,536,508 to Canal *et al.*
U.S. Patent No. 5,552,160 to Liversidge *et al.*
U.S. Patent No. 5,560,931 to Eickhoff *et al.*
U.S. Patent No. 5,560,932 to Bagchi *et al.*
U.S. Patent No. 5,565,188 to Wong *et al.*
U.S. Patent No. 5,569,448 to Wong *et al.*
U.S. Patent No. 5,571,536 to Eickhoff *et al.*
U.S. Patent No. 5,573,783 to Desieno & Stetsko.
U.S. Patent No. 5,580,579 to Ruddy *et al.*
U.S. Patent No. 5,585,108 to Ruddy *et al.*
U.S. Patent No. 5,587,143 to Wong.
U.S. Patent No. 5,591,456 to Franson *et al.*
U.S. Patent No. 5,622,938 to Wong.
U.S. Patent No. 5,662,883 to Bagchi *et al.*
U.S. Patent No. 5,665,331 to Bagchi *et al.*
U.S. Patent No. 5,718,919 to Ruddy *et al.*
U.S. Patent No. 5,747,001 to Wiedmann *et al.*
International Patent Publication No. WO 93/25190.
International Patent Publication No. WO 96/24336.
International Patent Publication No. WO 97/14407.
International Patent Publication No. WO 98/35666.
International Patent Publication No. WO 99/65469.
International Patent Publication No. WO 00/18374.
International Patent Publication No. WO 00/27369.
International Patent Publication No. WO 00/30615.

[0058] One of ordinary skill in the art will readily adapt the processes therein described to preparation of the hydrophobic substance in nanoparticulate form.

[0059] Illustrative examples are described below.

EXAMPLE 1

[0060] This example illustrates the improved systemic absorption of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione upon administration to the dermis.

[0061] The compound (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione has an estimated logP value of 1.62 using logKow software (Syracuse Research Corporation, North Syracuse, NY 13212; see also Meylan and Howard, *supra*). In accordance with the invention herein, this compound is shown to give higher plasma levels and improved pharmacokinetic parameters upon administration to the dermis than that produced upon subcutaneous administration.

[0062] Six Yucatan mini-pigs weighing 20-25 kg were used. Solutions of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione were prepared at 10 mg/mL concentrations at pH 5.5 in citrate/phosphate buffer with sufficient dextrose to achieve isotonicity received (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione by the following routes: (A) intravenous bolus, (B) subcutaneous injection, and (C) injection to the dermis by a microneedle array. A total of 6 animals were utilized in a full crossover design where each animal received a 1.0 mg dose by all administration routes in an injection volume of 0.1 mL.

[0063] The intravenous dose was administered an ear vein catheter. Subcutaneous delivery was through a standard 0.5 inch, 30 gauge needle. Delivery to the dermis was through a three point microneedle array having three 34 gauge needles with 7 mm spacing and 1 mm depth to right flank of the animal between the rib cage and the rear leg. Subcutaneous and intravenous administration was by manual injection seconds. Administration to the dermis was at a rate of 90 μL/min by a syringe pump.

[0064] The study design was a full crossover with each animal receiving intravenous, subcutaneous and dermal administration. Each animal received three treatments over a two-week period with a minimal washout period of 2 days between subsequent doses. Dosing was according to the schedule shown below in Table 2.

Table 2. Dosing Schedule*

Animal	Week 1		Week 2		Week 3		Week 4		Week 5
	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9
1	IV	ID	SC						
2	ID	SC	IV						
3				SC	IV	ID			
4				IV	ID	SC			
5							ID	SC	IV
6							SC	IC	ID

* IV represents intravenous administration, SC represents subcutaneous administration and ID represents administration to the dermis.

[0065] Blood samples were obtained from the vena cava access port immediately before dosing and at 5, 10, 15, 20, 30, 45, 60 minutes and 2, 3, 4, 6, 8, 10, 14 and 24 hours after administration. Timing was started at the cessation of injection for a given method. The venous samples were collected into EDTA containing Vacutainer tubes, centrifuged at approximately 1000 g for 10 minutes at 4°C. After centrifugation, the plasma layer was transferred to plastic storage vials and stored frozen at -70°C until assayed.

[0066] Assay of the pig plasma samples was performed by HPLC analysis. Results are shown below in Tables 3

Table 3. Plasma Concentrations (ng/mL) of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione Following Administration By Various Routes In Yucatan Mini-pigs.

TIME	IV*		ID		SC	
	Mean	SD	Mean	SD	Mean	SD
5 min	29.8	7.0	24.8	12.4	10.0	2.2
10 min	20.5	4.5	22.5	9.0	15.3	3.0
15 min	18.5	4.2	16.4	6.2	16.0	1.7
20 min	15.3	2.2	18.0	6.6	14.5	1.8
30 min	13.1	2.4	14.0	2.4	14.0	0.9
45 min	10.7	2.3	9.9	2.7	9.9	3.1
1 hr	9.1	1.5	9.0	1.6	8.9	1.4
2 hr	6.7	1.4	5.7	1.9	5.6	1.4
3 hr	2.8	2.6	4.2	1.5	4.1	2.0
4 hr	1.6	1.5	3.6	1.4	2.2	1.9
6 hr	2.6	4.1	0.4	1.0	1.6	3.3
8 hr	0	0	0	0	0.6	1.6
10 hr	0	0	0	0	0	0
14 hr	0	0	0	0	0	0
24 hr	0	0	0	0	0	0

* Drug was given by intravenous administration (IV), subcutaneous administration (SC) and by administration to the dermis (ID). The intravenous dose was administered to the 1.0 mg dosing subgroup into an ear vein.

[0067] As shown in Tables 3, administration into the dermis tended to produce higher plasma levels of drug than that produce upon subcutaneous administration. Analysis of the data by Heterogeneity of Regression analysis revealed that values obtained following administration to the dermis and intravenous administration were not different from each other, but different from values obtained following subcutaneous administration.

[0068] Pharmacokinetic parameters were estimated using Watson Drug Metabolism Laboratory Information Management System, version 6.2.0.02 (Innaphase

Corp., Philadelphia, PA). Parameters determined were the maximal plasma concentration, C_{max}, time to maximal plasma concentration T_{max}, area under the curve estimated to t = infinity, T_{max} and the half-life for decrease in plasma concentration, $T_{1/2}$.

[0069] Pharmacokinetic parameters are shown in Table 4 below.

Table 4. Mean Pharmacokinetic Parameters (± standard deviation) of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione Following Administration By Various Routes[a] In Yucatan Mini-pigs.

PARAMETER	1.0 mg Dose		
	IV (n=6)	ID (n=6)	SC (n=6)
Dose (μg/kg)	40.9 (3.2)	41.3 (3.9)	40.3 (3.4)
C_{max} (ng/mL)	29.8 (7.0)	26.7 (10.2)	16.9 (2.6)
T_{max} (hr)	0.083 (0.000)	0.139 (0.101)	0.222 (0.068)
$AUC_{(0-\infty)}$ (ng*hr/mL)	32.4 (8.2)	33.6 (9.0)	32.1 (9.2)
$T_{1/2}$ (hr)	1.45 (0.38)	1.61 (0.70)	1.5 (0.53)

[a] Drug was given by intravenous administration (IV), subcutaneous administration (SC) and by administration to the dermis (ID).

[0070] As shown in the table, the C_{max} values were consistently greater and the T_{max} values were consistently lesser following administration to the dermis than values for the same parameters obtained following subcutaneous administration of the hydrophobic substance, (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione.

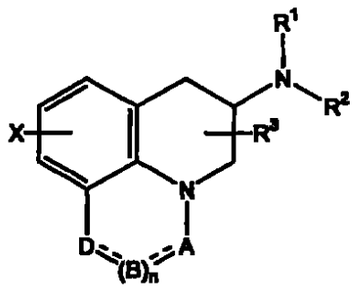
[0071] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

[0072] All references cited in this specification are hereby incorporated by reference. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art relevant to patentability. Applicant reserves the right to challenge the accuracy and pertinency of the cited references.

WHAT IS CLAIMED IS:

1. A method for systemic administration of a hydrophobic dopamine agonist to a mammal, the method comprising delivering the dopamine agonist to the dermis of the mammal, wherein improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

2. The method of claim 1 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above,

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$CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, $N\text{-}CH_3$;

(2) when n is 0, and

A is CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, $N\text{-}CH_3$; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(4) when n is 1, and

A is CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

3. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

4. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

5. The method of claim 1 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

6. The method of claim 5 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

7. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

8. The method of claim 7 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

9. The method of claim 8 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

10. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

11. The method of claim 1 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

12. The method of claim 11, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

13. The method of claim 10, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

14. The method of claim 10, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

15. The method of claim 10, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

16. The method of claim 1 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

17. The method of claim 16 wherein the delivering is through at least one hollow needle.

18. The method of claim 1 wherein the at least one hollow needle comprises an array of microneedles.

19. The method of claim 18 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

20. The method of claim 1 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

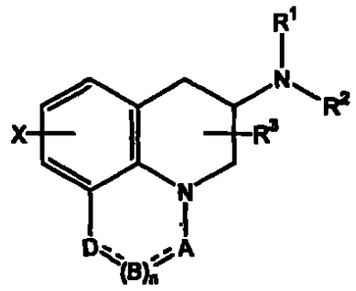
21. The method of claim 1 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

22. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal to obtain systemic absorption of the dopamine agonist from the dermis.

23. The method of claim 22 wherein improved systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis as

compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

24. The method of claim 23 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ---- is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

25. The method of claim 24 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

26. The method of claim 24 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

27. The method of claim 23 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

28. The method of claim 27 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

29. The method of claim 23 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

30. The method of claim 29 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

31. The method of claim 30 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

32. The method of claim 23 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

33. The method of claim 23 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

34. The method of claim 33, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

35. The method of claim 32, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

36. The method of claim 32, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

37. The method of claim 32, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

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38. The method of claim 23 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

39. The method of claim 38 wherein the delivering is through at least one hollow needle.

40. The method of claim 23 wherein the at least one hollow needle comprises an array of microneedles.

41. The method of claim 40 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

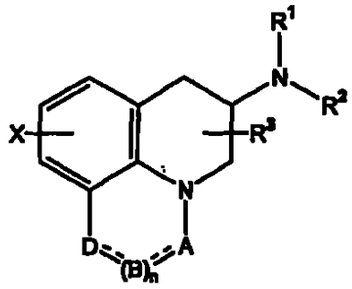
42. The method of claim 23 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

43. The method of claim 23 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

44. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal wherein systemic absorption of the dopamine agonist from the dermis is obtained.

45. The method of claim 42 wherein improved systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

46. The method of claim 43 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

47. The method of claim 44 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

48. The method of claim 44 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

49. The method of claim 43 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

50. The method of claim 47 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

51. The method of claim 43 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

52. The method of claim 49 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

53. The method of claim 50 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

54. The method of claim 43 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

55. The method of claim 43 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

56. The method of claim 53, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

57. The method of claim 52, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

58. The method of claim 52, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

59. The method of claim 52, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

60. The method of claim 43 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

61. The method of claim 58 wherein the delivering is through at least one hollow needle.

62. The method of claim 43 wherein the at least one hollow needle comprises an array of microneedles.

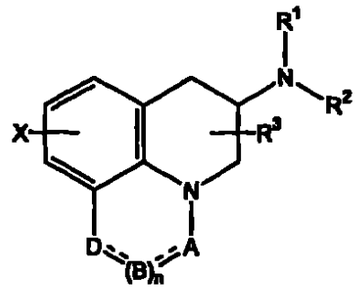
63. The method of claim 60 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Bellevi61lle spring, iontophoresis, or sonophoresis.

64. The method of claim 43 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

65. The method of claim 43 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

66. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal to achieve a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag}, and/or a substantially greater K_a as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

67. The method of claim 64 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ---- is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

68. The method of claim 65 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

69. The method of claim 65 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

70. The method of claim 64 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

71. The method of claim 68 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

72. The method of claim 64 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

73. The method of claim 70 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

74. The method of claim 71 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

75. The method of claim 64 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

76. The method of claim 64 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

77. The method of claim 74, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

78. The method of claim 73, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

79. The method of claim 73, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

80. The method of claim 73, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

81. The method of claim 64 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

82. The method of claim 79 wherein the delivering is through at least one hollow needle.

83. The method of claim 64 wherein the at least one hollow needle comprises an array of microneedles.

84. The method of claim 81 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

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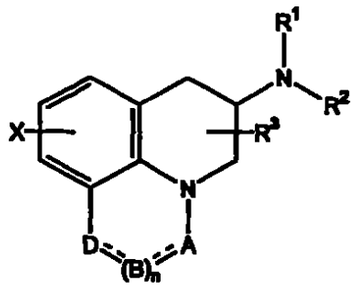
85. The method of claim 64 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

86. The method of claim 64 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

87. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal wherein a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag} and/or a substantially greater K_a is produced as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

88. The method of claim 85 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH,

CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

89. The method of claim 86 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

90. The method of claim 86 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

91. The method of claim 85 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

92. The method of claim 89 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

93. The method of claim 85 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

94. The method of claim 91 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

95. The method of claim 92 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

96. The method of claim 85 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

97. The method of claim 85 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

98. The method of claim 95, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

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99. The method of claim 94, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

100. The method of claim 94, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

101. The method of claim 94, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

102. The method of claim 85 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

103. The method of claim 85 wherein the delivering is through at least one hollow needle.

104. The method of claim 85 wherein the at least one hollow needle comprises an array of microneedles.

105. The method of claim 102 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

106. The method of claim 85 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

107. The method of claim 85 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

PERFIL FARMACOCINETICO MEJ RADO DE AGONISTAS DE DOPAMINA HIDROFOBICOS ADMINISTRADOS A LA DERMIS

REFERENCIA RECIPROCA A LAS SOLICITUDES RELACIONADAS

Esta solicitud es una continuación en parte de la solicitud de E.U.A. No. 09/897,801, presentada en junio 29 de 2001.

ANTECEDENTES DE LA INVENCION

CAMPO DE LA INVENCION

La presente invención se refiere a la administración de sustancias en la dermis y, más particularmente, a métodos, composiciones y dispositivos para administrar sustancias hidrofóbicas en la dermis. Dicha administración da como resultado absorción sistémica, la cual es mejor en comparación con la absorción lograda después de la administración subcutánea.

DESCRIPCION DE LA TECNICA RELACIONADA

Se ha reconocido desde hace mucho tiempo la importancia de administrar sustancias farmacéuticas tales como agentes de diagnóstico o

fármacos en una forma que dé como resultado buena absorción y eficacia biológica. Dicha eficacia biológica depende de la presentación sistémica de la sustancia reflejada en parámetros farmacocinéticos, y la acción del fármaco reflejada en mediciones farmacodinámicas (para una revisión, véase Cawello et al, *J. Clin. Pharmacol.* 37:65S-69S, 1997; Wasan et al., *Arch. Med. Res.* 24:395-401 1993; Ratain, *Semin. Oncol.* 19:8-13, 1992).

Las sustancias hidrofóbicas presentan un reto particular para lograr efectos biológicos deseados debido a las dificultades para preparar formulaciones de liberación (suministro) acopladas con la distribución significativa de estas sustancias en el tejido adiposo y su almacenamiento en dicho tejido (Steiner et al., *Drug Metab. Dispos. 19*:8-14, 1991; Xie et al, *Drug Metab. Dispos. 19*:15-19, 1991; Hough et al. *Life Sci. 58*:119-122, 1996). Como resultado, las sustancias hidrofóbicas no muestran con frecuencia más que absorción sistémica limitada tras la mayoría de las vías de administración convencionales. Las vías usadas comúnmente para administración sistémica, han implicado liberación subcutánea, intramuscular o intravenosa. Todas estas vías de administración pueden considerarse como administración transdérmica, es decir, liberación de sustancias a través de la piel a un sitio debajo de la piel. Típicamente, se han usado agujas convencionales para liberar sustancias transdérmicamente, aunque se han usado también otras alternativas.

Anatómicamente, la superficie exterior del cuerpo se forma de dos capas de tejido principales, una epidermis exterior y una dermis

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subyacente, las cuales constituyen en conjunto la piel (para una revisión, véase *Physiology, Biochemistry, and Molecular Biology of the Skin*, segunda edición, L. A. Goldsmith, ed., Oxford University Press, New York, 1991). La epidermis se subdivide en cinco capas o estratos de un grosor total entre 75 y 150 μm. Bajo la epidermis está la dermis, que contiene dos capas, una porción más exterior referida como la dermis papilar, y una capa más profunda referida como la dermis reticular. La dermis papilar contiene vastos plexos linfáticos y sangre de la microcirculación. En contraste, la dermis reticular es relativamente acelular y avascular, y se forma de tejido conectivo elástico y colagenoso denso. Bajo la epidermis y dermis está el tejido subcutáneo, referido también como la hipodermis, que se forma de tejido conectivo y tejido graso. El tejido muscular se sitúa bajo el tejido subcutáneo.

Como se indicó anteriormente, el tejido subcutáneo y el tejido muscular se han usado comúnmente como sitios para administración de sustancias farmacéuticas. Sin embargo, la dermis rara vez se ha elegido como un sitio para la administración de sustancias, y esto puede deberse, por lo menos en parte, a la dificultad para colocar en forma precisa la aguja en la dermis. Además, aún cuando se sabe que la dermis, en particular la dermis papilar, tiene un alto grado de vascularidad, no se ha apreciado hasta ahora que pudiera sacarse ventaja de este grado de vascularidad para lograr un perfil de absorción mejorado para sustancias hidrofóbicas, en comparación con el que se logra después de la administración subcutánea. Esto es porque las sustancias de fármaco pequeñas típicamente se absorben rápidamente

después de la administración en el tejido subcutáneo, el cual se ha elegido mucho más fácilmente y en forma que se pueda predecir de lo que la dermis ha sido. Por otra parte, las sustancias hidrofóbicas, así como grandes moléculas tales como las proteínas, típicamente no son absorbidas rápida o enteramente después de las administraciones subcutáneas. Puesto que las sustancias hidrofóbicas tienden a separarse en el tejido adiposo subcutáneo, es de esperarse que la absorción de estas sustancias en el sistema vascular sea limitada después de la administración subcutánea (Walder, *Immunopharmacol. Immunotoxicol. 13*:101-119, 1991). Se esperaría también que las grandes proteínas sean absorbidas lentamente después de la administración subcutánea, y se ha reportado con frecuencia que la biodisponibilidad es altamente variable e incompleta (Porter et al., *Adv. Drug. Deliv. Rev. 50*:157-171, 2001). Además, las proteínas hidrofóbicas pueden mostrar absorción reducida después de la administración subcutánea medida mediante parámetros farmacocinéticos normales, en comparación con valores obtenidos para proteínas que no son hidrofóbicas (véase, por ejemplo, Thomsen et al., *Pharmacol. Toxicol. 74*:351-358, 1994). A pesar de esto, no se han administrado típicamente sustancias hidrofóbicas en la dermis.

Numerosos reportes en la literatura han reportado lo que se ha descrito como administración "intradérmica". Sin embargo, dichas referencias han usado con frecuencia el término "intradérmico" de acuerdo a su significado usado comúnmente de "intracutáneo", es decir, dentro de la sustancia de la piel. Esto incluiría, principalmente, el tejido subcutáneo. En

otras referencias, se pretende que la denominada colocación "intradérmica" de sustancias inyectadas logre no más que la administración local de la sustancia, y no se ha hecho intento alguno por lograr biodisponibilidad sistémica de las sustancias inyectadas.

Una de dichas alternativas para lograr la administración local de sustancias, se ha usado habitualmente en la prueba de tuberculina de Mantoux. En este procedimiento, un derivado purificado de proteína se inyecta, a un ángulo somero, a la superficie de la piel usando una aguja de calibre 27 ó 30 (Flynn et al, *Chest 106*: 1463-5, 1994). Sin embargo, un alto grado de incertidumbre en la colocación de la inyección puede dar como resultado algunos resultados de prueba falsos negativos. Además, la prueba ha implicado una inyección localizada para inducir una respuesta en el sitio de inyección, y la alternativa de Mantoux no ha llevado a la inyección de sustancias en la dermis con el propósito de lograr la liberación sistémica de sustancias.

En forma similar, se han usado inyecciones "intradérmicas" locales de fármacos anestésicos para disminuir el dolor asociado con la inserción del catéter i.v., y con la suturación de laceraciones (véase, por ejemplo, Criswell et al., *Anaesthesia 46*:691-692, 1991; Anderson et al., *Ann. Emerg. Med. 19*:519-22, 1990). Sin embargo, se pretende que dicho uso de fármacos anestésicos locales sea localizado en el sitio de inyección, y no se ha logrado la liberación sistémica de los agentes anestésicos locales.

Algunos grupos han reportado por administración sistémica lo

que se ha caracterizado como inyección "intradérmica". En uno de dichos reportes, se realizó un estudio comparativo de inyección subcutánea y lo que se describió como inyección "intradérmica" (Autret et al, *Therapie 46*:5-8, 1991). La sustancia farmacéutica puesta a prueba fue calcitonina, una proteína de un peso molecular de aproximadamente 3600, que es altamente soluble én agua en forma inyectable. En forma similar, Bressolle et al., administraron la sustancia soluble en agua, ceftazidima de sodio, en lo que se caracterizó como inyección "intradérmica" (Bressolle et al. *J. Pharm. Sci. 82*:1175-1178, 1993). Ninguno de estos estudios provee información profética alguna acerca de la absorción de sustancias hidrofóbicas después de la administración a la dermis.

Otro grupo reportó lo que se ha descrito como un dispositivo de liberación de fármaco "intradérmico" (véase patente de E.U.A. No. 5,997,501 a Gross et al.). Se indicó que la inyección es a un régimen lento, y el sitio de inyección se reservó para ser en alguna región bajo la epidermis, es decir, la interfaz entre la epidermis y la dermis o el interior de la dermis o el tejido subcutáneo. Esta referencia describe la administración con un dispositivo particular mediante infusión a regímenes lentos que no se esperaría muestren alguna absorción sistémica mejorada medida mediante parámetros farmacocinéticos, en comparación con la que se obtiene después de la administración subcutánea. Esto es porque a regímenes de infusión lentos, el régimen de infusión sería el régimen de absorción limitativo definitivo, y no las barreras de absorción del tejido. Como tal, no es de esperarse que la

absorción dérmica sea mayor que la absorción subcutánea.

De esta manera, existe la necesidad continua de métodos y dispositivos eficaces para administrar sustancias hidrofóbicas en una forma que logre absorción sistémica rápida y completa de los compuestos.

BREVE DESCRIPCION DE LA INVENCION

Por consiguiente, el inventor de la presente ha tenido éxito al descubrir una alternativa para administrar sustancias hidrofóbicas en la cual se logra absorción mejorada, en comparación con la que se logra después de la administración subcutánea de las sustancias. La absorción mejorada se indica mediante una mejora en por lo menos un parámetro farmacocinético o farmacodinámico. La alternativa implica liberar selectivamente las sustancias hidrofóbicas en la dermis. La liberación de la sustancia hidrofóbica es hacia la dermis, o en una región en estrecha proximidad a la dermis, de modo que la absorción ocurra predominantemente en la dermis. De preferencia, la sustancia hidrofóbica se administra mediante bolo, es decir, dentro de un período breve de alrededor de 10 minutos a aproximadamente 15 minutos o menos y, más preferiblemente, dentro de 2 minutos o menos. En forma sorprendente, dicha liberación hacia la dermis da como resultado una mejora en las mediciones farmacocinéticas y/o farmacodinámicas en comparación con la que se logra después de la administración subcutánea.

De esta manera, la presente invención provee, en una

modalidad, un método para la administración sistémica de una sustancia a un mamífero. De preferencia, el mamífero es un humano, aunque animales de compañía tales como perros y gatos, animales de granja tales como cerdos y vacas, animales exóticos tales como animales del zoológico, y similares, se incluyen también dentro del alcance de la presente invención.

El término "hidrofóbico", como se usa con respecto a una sustancia administrada en la dermis o tejido subcutáneo, se usa para indicar que la sustancia tiende a separarse preferiblemente en compartimentos lipofílicos tales, que puede encontrarse en tejidos adiposos subcutáneos, más que en fluidos extracelulares acuosos. La hidrofobicidad de una sustancia puede evaluarse mediante métodos normales tales como, por ejemplo, determinando el coeficiente de distribución de aceite-agua, de preferencia, el coeficiente de distribución de *n*-octanol/agua (véase, por ejemplo, Buchwald, *Curr Med Chem* 5:353-380, 1998). Los valores se expresan típicamente como la hidrofobicidad o valor logarítmico del coeficiente de separación, logP, bajo condiciones fisiológicas adecuadas. Dichas condiciones dependerán de las condiciones de la región de administración objetivo en el mamífero, incluyendo temperatura, pH, concentración, y similares. Asimismo, el logaritmo de los coeficientes de separación de octanol-agua puede calcularse usando una variedad de programas de cálculo, tal como el desarrollado por Syracuse Research Corporation (Meylan y Howard, *J. Pharm. Sci. 84*: 83-92, 1995).

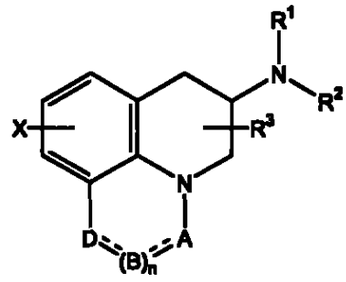
Un valor umbral de $logP_{oct}$, que se correlaciona con la separación en el tejido adiposo, está entre 1.0 y 2.0, como ha sido mostrado por Steiner

et al., para compuestos de barbiturato (Steiner et al., *Drug Metabolism and Disposition 19*:8-14, 1991; véase, en particular, la figura 4). Esto se ha mostrado también para un número de fármacos básicos (Betschart et al, *Xenobiotica 18*:113-121, 1988; véase, en particular, la figura 2). De esta manera, las sustancias hidrofóbicas de la presente invención tienen un valor de logP umbral mayor de 1.00, de preferencia de por lo menos aproximadamente 1.5 o más. Se ha mostrado una relación lineal entre la captación por el tejido adiposo y valores de logP de hasta 5 y más, para algunos compuestos (Betschart et al., citado anteriormente). De esta manera, en ciertas modalidades, es deseable que el compuesto hidrofóbico tenga un $logP_{oct}$ mayor de 1.5, es decir, de por lo menos alrededor de 2.0 o más, por lo menos aproximadamente 2.5 o más, por lo menos alrededor de 3.0 o más, por lo menos aproximadamente 3.5 o más, por lo menos alrededor de 4.0 o más, o por lo menos aproximadamente 5.0 o más.

Las sustancias hidrofóbicas de la presente invención pueden ser fármacos moleculares pequeños o agentes de diagnóstico o grandes moléculas tales como proteínas, polisacáridos u otros compuestos poliméricos. Las sustancias hidrofóbicas de la presente invención incluyen como ejemplos no limitativos, hidantoínas anticonvulsivantes, ácidos barbitúricos, inhibidores de proteasa de VIH, nucleósidos antivirales, compuestos tricíclicos que contienen nitrógeno para tratamiento del sistema nervioso central y condiciones de disfunción sexual, así como numerosas otras sustancias hidrofóbicas. La invención es particularmente aplicable a

compuestos tricíclicos que contienen nitrógeno útiles para tratar disfunción sexual en hombres y mujeres, como se describe en la publicación de patente internacional No. WO 00/40226. Los compuestos de esta clase se describieron primero en la patente de E.U.A. No. 5,273,975 (el documento WO 00/40226 y la patente de E.U.A. No. 5,273,975, se incorporan en su totalidad en la presente como referencia).

Dichos compuestos son de la fórmula (I):



(I)

o sales farmacéuticamente aceptables de los mismos, en donde:

R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo;

X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6};

A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N;

B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3, y n

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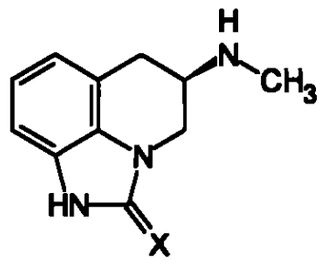
es 0 ó 1; y

D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3;

con varias condiciones indicadas en el documento WO 00/40226.

Compuestos preferidos útiles en los métodos de la presente invención, son los descritos genéricamente o específicamente en la patente de E.U.A. No. 5,273,975 citada anteriormente. Compuestos especialmente preferidos, son los de fórmula (II):



(II)

en donde X es O u S.

La absorción sistémica mejorada producida por la liberación hacia la dermis, puede medirse mediante cualquiera de un número de parámetros farmacocinéticos y/o farmacodinámicos normales tales como, por ejemplo, aumento en biodisponibilidad, disminución en $T_{máx}$, aumento en $C_{máx}$, disminución en T_{lag}, o similares. Por biodisponibilidad se entiende la cantidad total de una dosificación determinada que llegó al compartimento sanguíneo. Esta se mide en general como el área bajo la curva en una gráfica de concentración contra tiempo, es decir, AUC. Sin embargo, la biodisponibilidad incluye teóricamente la cantidad total que llega al compartimento sanguíneo durante un período infinito después de la dosificación; como asunto práctico,

la biodisponibilidad se mide durante un intervalo de tiempo finito de varias horas después de la dosificación tal como, por ejemplo, alrededor de 2 horas, aproximadamente 4 horas, alrededor de 6 horas, aproximadamente 8 horas, alrededor de 12 horas, aproximadamente 14 horas o alrededor de 24 horas después de la dosificación, o más tiempo.

Por "tiempo de demora" o T_{lag} se entiende la demora entre la administración de un compuesto y el tiempo para niveles en plasma o sangre medibles o detectables. Aunque el T_{lag} dependerá de la sensibilidad del método de prueba que mide o detecta los niveles de una sustancia en sangre o plasma, la disminución en T_{lag} depende del método de prueba debido a que el mismo método de prueba se usa para medir los niveles en sangre o plasma bajo las condiciones del comparador que muestra la disminución en T_{lag}. Por ejemplo, el mismo sistema de prueba se usa para comparar niveles en plasma después de la administración subcutánea y después de la administración de una sustancia hacia la dermis. Un tiempo más corto para lograr niveles detectables de la sustancia, después de administración en la dermis, en comparación con la administración subcutánea, indica absorción mejorada.

$T_{máx}$ es un valor que representa el tiempo para lograr la concentración máxima del compuesto en sangre, y $C_{máx}$ es la concentración máxima en sangre alcanzada con una dosis y método de administración determinados. El tiempo para el inicio de acción se relaciona con T_{lag}, $T_{máx}$ y $C_{máx}$, puesto que todos estos parámetros influyen sobre el tiempo necesario para lograr una concentración en sangre (o tejido objetivo) necesaria para

lograr un efecto biológico. La $T_{máx}$ y la $C_{máx}$ pueden determinarse mediante inspección visual de resultados gráficos, y pueden proveer con frecuencia información suficiente para comparar dos métodos de administración de un compuesto. Sin embargo, los valores numéricos pueden determinarse en forma más precisa mediante análisis usando modelos cinéticos (como se describe más adelante) y/u otros medios conocidos por los expertos en la técnica.

La liberación en la dermis puede ser con cualquiera de una amplia variedad de dispositivos que producen un microporo cutáneo tal como se produce mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases. Dichos dispositivos son referidos en la presente como dispositivos de poración, en particular dispositivos de microporacion, o dispositivos de acceso dérmico. De preferencia, la liberación es a través de una o más agujas huecas, aunque agujas o inyección balística de fluidos o polvos libre de agujas en el espacio ID, iontoforesis, electroporación o deposición directa de fluidos, sólidos u otras formas de dosificación en la piel, y similares, están también dentro del alcance de la presente invención, en tanto por lo menos un microporo cutáneo sea establecido por el dispositivo de liberación.

Los métodos de la presente invención pueden incluir, en una modalidad, una liberación selectiva de la sustancia hidrofóbica hacia la dermis. Dicha liberación selectiva implica colocación intencional de la sustancia en la dermis o en la región de la dermis que dará como resultado o

permite el acceso hacia la dermis y la absorción no impedida de la sustancia en la misma, en comparación con la colocación en cualquier otra región de la piel. La liberación selectiva puede comprender, totalmente o en parte, un reconocimiento de que la liberación de la sustancia es hacia la dermis. En un aspecto de esta modalidad, la liberación de la sustancia hacia la dermis da como resultado absorción sistémica y, de preferencia, se logra absorción sistémica mejorada. Dicha absorción sistémica mejorada puede comprender una biodisponibilidad sustancialmente mayor y/o una $C_{máx}$ sustancialmente mayor, y/o un $T_{máx}$ sustancialmente más corto y/o un T_{lag} sustancialmente más corto. En una variación de la modalidad, la liberación se usa para lograr absorción sistémica y, de preferencia, absorción sistémica mejorada. Dicha liberación selectiva para obtener absorción sistémica mejorada puede comprender, totalmente o en parte, la medición de uno o más parámetros farmacocinéticos que muestren dicha mejora.

Entre las varias ventajas logradas mediante la presente invención, puede observarse por lo tanto la provisión de una nueva vía de administración parenteral de sustancias hidrofóbicas que puede lograr la liberación sistémica de las sustancias; la provisión de un método de administración adecuado para lograr inicio de acción rápido de sustancias hidrofóbicas; la provisión de métodos adecuados para obtener administraciones repetidas de bolo que simulen la liberación rápida y pulsátil de hormonas naturales; la provisión de métodos que permitan la administración intermitente y/o pulsátil de hormonas hidrofóbicas o miméticos

que eviten cualquier subregulación del receptor inducida por los niveles continuos de las hormas en sangre; la provisión de un modo de administración que logre una alta absorción y biodisponibilidad que permita que se use menos fármaco activo y una reducción en costos y una probabilidad disminuida de efectos secundarios; la provisión de un método de administración de una sustancia hidrofóbica que pueda lograr niveles mayores en sangre que los logrados con la administración subcutánea del mismo nivel de dosis; la provisión de un método administración que produzca incrementos de eficacia de la sustancia sin alterar los regímenes de eliminación sistémicos y sin alterar los efectos farmacodinámicos; la provisión de un método que evite que la sustancia sea atrapada en los compartimentos lipofílicos del tejido subcutáneo para producir un efecto de depósito; la provisión de un método que sea sujeto a un régimen de dosis regulado como resultado de absorción rápida de la sustancia administrada; y la provisión de un método de administración cutánea que cuando se implemente con un dispositivo de aguja hueca, coloque la sustancia directamente en la dermis para evitar la degradación metabólica y/o la actividad inmunológica que pueden ocurrir en la epidermis.

DESCRIPCION DETALLADA DE LA INVENCION

De conformidad con la presente invención, se ha descubierto que la administración de una sustancia hidrofóbica hacia la dermis, da como

resultado absorción sistémica mejorada de la sustancia.

Las sustancias hidrofóbicas de la presente invención tienden a ser de baja solubilidad en agua o a ser insolubles en agua, pero solubles en solventes no polares. La hidrofobicidad de una sustancia puede evaluarse mediante métodos normales tales como, por ejemplo, determinando el coeficiente de distribución de aceite-agua, de preferencia, el coeficiente de distribución de *n*-octanol/agua (véase, por ejemplo, Buchwald, *Curr Med Chem* 5:353-380, 1998). La distribución de aceite-agua, es la relación de concentración de un compuesto en una fase de solvente no polar inmiscible en agua, tal como *n*-octanol, a la concentración en una fase acuosa en contacto con la fase de solvente. Los valores se expresan típicamente como el valor logarítmico del coeficiente de separación, logP, bajo condiciones fisiológicas adecuadas. Dichas condiciones dependerán de las condiciones de la región de administración objetivo en el mamífero, incluyendo temperatura, pH, concentración, y similares.

Para sustancias que son ionizables, los valores de pK o el logaritmo negativo de la constante de disociación de dichas sustancias, son una consideración, y estos valores se determinan a veces al mismo tiempo que se determina la hidrofobicidad. Esto es porque el coeficiente de separación es la relación de concentración de una sustancia como la molécula neutra en un solvente inmiscible en agua a su concentración en una fase acuosa. Por lo tanto, es importante conocer la cantidad de especies neutras presentes, y ésta puede determinarse mediante el pK de la sustancia y el pH

de la solución acuosa. El pKa es el logaritmo negativo de la constante de equilibrio de un ácido, y el pKb es el logaritmo negativo de la constante de equilibrio de una base. Como asunto práctico, un ácido que tenga un pKa de una o más unidades mayores que 7.4, es decir, 8.4 o más, o una base que tenga un pKb de una o más unidades menores que 7.4, es decir, 6.4 o menores, está predominantemente en forma de la molécula neutra a un pH fisiológico de 7.4, y esta forma neutra se separará sustancialmente en la fase oleosa en una prueba de distribución de aceite-agua.

Otro factor que afectará el valor medido del logP, además del pH, es el solvente no polar particular usado en la fase oleosa. Típicamente, el *n*-octanol es el solvente no polar debido a que esta sustancia tiene una relación de carbono: oxígeno que es similar a la del material lipídico en grasas animales. De esta manera, se piensa que el coeficiente de separación de *n*-octanol refleja la distribución de una sustancia administrada a un sujeto en regiones del cuerpo que contienen una cantidad significativa de tejido adiposo.

El coeficiente de separación de una sustancia puede medirse mediante cualquiera de un número de métodos conocidos en la materia. Estos incluyen, sólo con fines ilustrativos, métodos potenciométricos tales como con PCA101 de dispositivos GlpKa(TM) (Sirius Analytical Instruments, Ltd, East Sussex, Reino Unido), que miden el pKa y el coeficiente de separación, métodos de sonda de filtración (Tomilinson, *J. Pharm. Sci* 71:602-604, 1982); métodos de CLAR de fase invertida (véase, por ejemplo, Valko et al., *Curr. Med. Chem.* 8:1137-1146, 2001), métodos de agitación en matraz, métodos

predictivos (véase, por ejemplo, Buchwald et al., *Curr. Med. Chem.* 5:353-380, 1998), y similares.

Se ha mostrado que el LogP se relaciona con la solubilidad acuosa de acuerdo a la siguiente ecuación (Hansch et al., *J. Org. Chem.* 33:347-350, 1968):

$$\log S_w = - 1.34 \log P_{oct} + 0.99$$

en donde $\log S_w$ es la solubilidad molar, y $\log P_{oct}$ es el coeficiente de separación de agua-aceite. Mediante el uso de esta ecuación, pueden calcularse los valores para $\log P_{oct}$ a partir de datos de solubilidad.

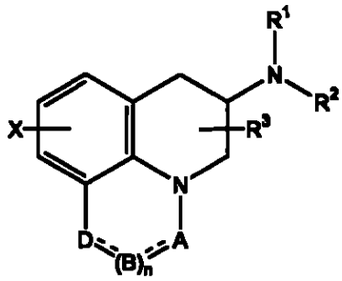
Las sustancias hidrofóbicas de la presente invención muestran de preferencia un coeficiente de separación de *n*-octanol-agua de por lo menos aproximadamente 1.5 o más, más preferiblemente por lo menos alrededor de 2.0 o más, y en ciertas modalidades, de preferencia por lo menos aproximadamente 2.5 o más, por lo menos alrededor de 3.0 o más, por lo menos aproximadamente 3.5 o más, o por lo menos alrededor de 4.0 o más.

Las sustancias hidrofóbicas que pueden liberarse en la dermis de conformidad con la presente invención, se usan para incluir sustancias farmacéutica o biológicamente activas que incluyen agentes de diagnóstico, fármacos y otras sustancias que proveen beneficios terapéuticos o de salud tales, como por ejemplo, nutracéuticos.

Las sustancias hidrofóbicas de la presente invención pueden ser fármacos moleculares pequeños o agentes de diagnóstico o grandes moléculas tales como proteínas, polisacáridos u otros compuestos

poliméricos. Las sustancias hidrofóbicas de la presente invención incluyen como ejemplos no limitativos, hidantoínas anticonvulsivantes, ácidos barbitúricos, inhibidores de proteasa de VIH, nucleósidos antivirales, inhibidores de ciclooxigenasa, compuestos tricíclicos que contienen nitrógeno para tratamiento del sistema nervioso central y condiciones de disfunción sexual, así como numerosas otras sustancias hidrofóbicas.

La invención es particularmente aplicable a compuestos tricíclicos que contienen nitrógeno de la fórmula (I):



(I)

o sales farmacéuticamente aceptables de los mismos, en donde:

R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo;

X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6};

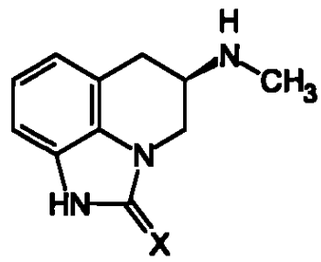
A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N;

B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3, y n es 0 ó 1; y

D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3;

con varias condiciones indicadas en el documento WO 00/40226.

Compuestos especialmente preferidos, son los de fórmula (II):



(II)

en donde X es O (sumanirol) o S (compuesto III) (véase el documento WO 00/40226 y la patente de E.U.A. No. 5,273,975, los cuales se incorporan en su totalidad en la presente como referencia). Particularmente preferidos, son los compuestos de la serie útiles para el tratamiento de disfunción sexual, especialmente (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona, y sales farmacéuticamente aceptables, así como sumanirol, que es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-ona, y sales farmacéuticamente aceptables.

Aceptabilidad farmacéutica se refiere a las propiedades que proveen conveniencia para administración a un sujeto, incluyendo requisitos de agencias gubernamentales, aceptación por el paciente y requisitos químicos y físicos que permiten la fabricación, estabilidad, biodisponibilidad en el sujeto, y similares. Sales farmacéuticamente aceptables, incluyen sales de

los siguientes ácidos: maleico, metansulfónico, clorhídrico, bromhídrico, sulfúrico, fosfórico, nítrico, benzoico, cítrico, tartárico, fumárico, y similares.

Se calculó que el LogP de la (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona es de 1.62 usando el programa logKow (Syracuse Research Corporation, North Syracuse, NY 13212; véase también Meylan y Howard, citado anteriormente). De conformidad con la presente invención, se esperaría que este compuesto produzca valores de $C_{máx}$ mayores y valores de $T_{máx}$ más cortos después de administración a la dermis, en comparación con los que se obtienen después de la administración subcutánea.

Otras sustancias hidrofóbicas dentro del alcance de la presente invención, incluyen los ejemplos no limitativos de hidantoínas anticonvulsivantes, ácidos barbitúricos, inhibidores de proteasa de VIH, inhibidores de ciclooxigenasa, nucleósidos antivirales y pineno y sus derivados, como se muestra en el cuadro 1 siguiente:

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CUADR 1

Valores de LogP de sustancias hidrofóbicas

Compuesto	$LogS_w$ (moles/L)	$LogP_{oct}$*	Referencia
Hidantoínas anticonvulsivantes			
5,5-difenilhidantoína	-4.10	3.80	Stella et al, *J. Pharm. Sci*, 88:775-79, 1999
3-pentanoiloximetil-5,5-difenilhidantoína	-4.68	4.23	
3-octanoloximetil-5,5-difenilhidantoína	-6.52	5.60	
Anetol tritiona	-5.80	5.07	
ditioletiona	-2.48	2.59	
5-fenilditioletiona	-5.64	4.95	
dimetiltioletiona	-3.42	3.29	
Acidos barbitúricos			
Acido 5,5-dimetilbarbitúrico	-1.74	2.04	Prankerd et al *Int. J. Pharm.* 112:1-15,1994
Acido 5-Me-5-etilbarbitúrico	-1.23	1.66	
Acido 5-Me-5-alilbarbitúrico	-1.16	1.60	
Acido 5-Me-5-fenilbarbitúrico	-2.38	2.51	
Acido 5-Me-5-(3-metilbut-2-enil)barbitúrico	-2.60	2.68	
Acido 5,5-dietilbarbitúrico	-1.40	1.78	
Acido 5-Et-5-iPr-barbitúrico	-2.15	2.34	
Acido 5-Et-5-alil-barbitúrico	-1.61	1.64	
Acido 5-Et-5-fenil-barbitúrico	-2.32	2.47	
Acido 5-Et-5-(3-metilbut-2-enil)barbitúrico	-2.25	2.42	
Acido 5,5-difenilbarbitúrico	-4.20	3.87	
Acido 5,5-di-iPr-barbitúrico	-2.77	2.81	
Acido 5-iPr-5-alil-barbitúrico	-1.71	2.01	
Acido 5-iPr-5-(3-metilbut-2-enil)-barbitúrico	-2.59	2.67	
Acido 5-tBu-5-(3-metilbut-2-enil)-barbitúrico	-3.55	3.39	
Acido 5-dialil-barbitúrico	-2.08	2.29	
Acido 5-alil-5-fenilbarbitúrico	-2.37	2.51	
Acido 5-dietil-2-tiobarbitúrico	-2.17	2.36	

Acido 5-Et-5-(1-metilbutil)-2-tiobarbitúrico	-3.68	3.49	
Acido 5,5-(CH2)2-barbitúrico	-1.89	2.15	
Acido 5,5-(CH2)3-barbitúrico	-1.66	1.98	
Acido 5,5-(CH2)4-barbitúrico	-2.35	3.97	
Acido 5,5-(CH2)5-barbitúrico	-3.06	3.02	
Acido 5,5-CH2)6-barbitúrico	-3.17	3.10	
Acido 5,5-(CH2)7-barbitúrico	-2.98	2.96	
Acido 5,5-(CH2)10-barbitúrico	-4.59	4.16	
Acido 5,5-(CH2)5-2-tiobarbitúrico	-3.46	3.32	
Acido 5,5-(CH2)11-barbitúrico	-5.80	5.07	
Inhibidotes de proteasa de VIH			
Didanosina	-0.90	1.48	Williams et al., *Adv. Drug Del. Rev.* 39:211-238, 1999
Delavirdina	-4.76	4.29	
Efavirenz	-4.57	4.15	
Indinavir	-3.94	3.68	
Ritonavir	-5.16	4.52	
Amprenavir	-4.00	3.72	
Saquinavir	-4.33	3.97	
N-(3{(1R)-1-[(6R)-4-hidroxi-2-oxo-6-fenetil-6-propil-5,6-dihidro-2H-piran-3-il]propil}fenil)-5-(trifluorometil)-2-piridinsulfonamida	-8.00*	6.71	log P calculado usando el programa SRC (Meylan, et al. *J.Pharm. Sci. 84:* 83-92, 1995)
Nucleósidos antivirales			
N2-acetilaciclovir	-1.92	2.17	Kristl, *Med.Res. Rev. 7*:417-440, 1999.
O-acetilaciclovir	-0.86	1.38	
N2,O-diacetilaciclovir	-2.70	2.75	
Pineno y derivados			
a-pineno	-3.66	3.47	Fichan et al., *J. Chem. Eng. Data 44*:773-777, 1999
B-pineno	-3.91	3.66	
limoneno	-3.41	3.28	
Mirceno	-3.58	3.41	
Borneol	-2.62	2.69	
Alcohol de fenchilo	-2.27	2.43	
Oxido de pineno	-2.59	2.67	
a-ionona	-3.06	3.02	

carveol	-1.88	2.14	
linalool	-2.00	2.23	
a-terpineol	-1.91	2.16	
Carvona	-1.67	1.99	
Inhibidores de ciclooxigenasa			log P calculado usando el programa SRC (Meylan, et al. *J.Pharm. Sci. 84:* 83-92, 1995.)
Celecoxib	-3.66*	3.47	
Valdecoxib	-2.59*	2.67	
Parecoxib	- 3.16*	3.10	

El $LogP_{oct}$ se calculó como $logP_{oct} = (0.99 - logS_w)/1.34$, salvo en donde se indica de otra manera.

El perfil farmacocinético para compuestos individuales variará de acuerdo a las propiedades químicas de los compuestos. Por ejemplo, se espera que los compuestos que son moléculas hidrofóbicas pequeñas que tienen un peso molecular no mayor de 1000 Daltons, muestren cambios significativos en comparación con los métodos parenterales tradicionales de administración, tales como inyección intramuscular, subcutánea o subdérmica. Además, se espera que los compuestos que son hidrofóbicos y relativamente grandes, teniendo un peso molecular de por lo menos 1000 Daltons, así como compuestos más grandes de por lo menos 2000 Daltons, por lo menos 4000 Daltons, por lo menos 10,000 Daltons y más grandes, muestren los cambios más significativos en comparación con los métodos parenterales tradicionales de administración, tales como inyección intramuscular, subcutánea o subdérmica.

Se piensa que el perfil de absorción mejorado será particularmente evidente para sustancias que no son bien absorbidas cuando se inyectan subcutáneamente tales como, por ejemplo, sustancias hidrofóbicas y, en particular, macromoléculas hidrofóbicas. Las macromoléculas y, en particular, las macromoléculas hidrofóbicas son, en general, no bien absorbidas subcutáneamente, y esto puede deberse no sólo a su tamaño respecto al tamaño de poro capilar, sino puede deberse también a su difusión lenta a través del intersticio debido a su tamaño e hidrofobicidad. Se entenderá que las macromoléculas hidrofóbicas pueden poseer dominios hidrofóbicos discretos. En contraste, las moléculas pequeñas que son hidrofílicas son en general bien absorbidas cuando se administran subcutáneamente, y es posible que no se observe perfil de absorción mejorado alguno después de su inyección en la dermis, en comparación con la absorción después de la administración subcutánea.

Las sustancias hidrofóbicas dentro del alcance de la presente invención, pueden incluir conjugados que se enlazan covalentemente. Dichos conjugados pueden incluir los ejemplos no limitativos de moléculas de alto o bajo peso molecular conjugadas con polietilenglicol (PEG) y otros polímeros (para una revisión, véase Veronese, *Biomaterials* 22:405-417, 2001). La unión covalente del PEG a una proteína puede aumentar ampliamente la vida media de la proteína en la sangre. Conjugados de proteína-proteína, es decir, proteínas de fusión, se incluyen también dentro del alcance de la presente invención tales como, por ejemplo, conjugados de Fv de cadena sencilla (sFv)

con proteínas efectoras (para una revisión, véase Huston et al, *Int. Rev. Immunol* 10: 195-217, 1993). Anticuerpos Fv de cadena sencilla pueden conjugarse también con moléculas pequeñas tales como marcas de formación de imágenes (véase, por ejemplo, Begen et al, *Nat. Med.* 2:979-984, 1996), y dichos conjugados están también dentro del alcance de la presente invención.

Por "farmacocinética mejorada", se entiende que se logra una mejora del perfil farmacocinético según se mide, por ejemplo, mediante parámetros farmacocinéticos normales tales como tiempo para la concentración máxima en plasma ($T_{máx}$), la magnitud de la concentración máxima en plasma ($C_{máx}$), o el tiempo para inducir una concentración mínimamente detectable en sangre o plasma (T_{lag}). Por perfil de absorción mejorado, se entiende que la absorción se mejora o es mayor, según se mide mediante dichos parámetros farmacocinéticos. La medición de los parámetros farmacocinéticos y la determinación de las concentraciones mínimamente efectivas, se llevan a cabo habitualmente en la técnica. Se considera que los valores obtenidos son mejorados en comparación con una vía de administración normal tal como, por ejemplo, administración subcutánea o administración intramuscular. En dichas comparaciones, se prefiere, aunque no es necesariamente esencial, que la administración en la dermis y la administración en el sitio de referencia tal como el tejido subcutáneo, impliquen los mismos niveles de dosis, es decir, la misma cantidad y concentración de fármaco, así como el mismo vehículo o portador. La administración hacia el sitio de referencia puede ser a un régimen del método

de administración de bolo, y/o la administración puede ser al mismo régimen que la administración hacia la dermis, ya sea a un régimen de administración de bolo o a un régimen de administración de infusión más lento. Se prefiere la administración hacia el sitio de referencia a un régimen de administración de bolo para lograr una mejora comparativa de absorción sistémica, puesto que dicha administración de bolo de sustancias hidrofóbicas hacia el tejido subcutáneo muestra un régimen disminuido de absorción sistémica, en comparación con la absorción de sustancias que son hidrofílicas o sustancias que son menos hidrofóbicas que la sustancia de prueba (véase, por ejemplo, Fuji et al, *Exp. Anim. 48*:241-246, 1999). De esta manera, la mejora en la absorción sistémica reflejada en los parámetros farmacocinéticos, es más pronunciada después de la administración a la dermis, en comparación con los valores medidos después de la administración subcutánea de bolo.

La comparación puede ser también al mismo régimen de administración en términos de cantidad y volumen por unidad de tiempo. De esta manera, por ejemplo, la administración de una sustancia farmacéutica determinada en la dermis a una concentración tal como 100 µg/ml, y el régimen de 100 µL por minuto durante un período de 5 minutos se compararía, de preferencia, con la administración de la misma sustancia farmacéutica en el espacio subcutáneo a la misma concentración de 100 µg/ml y el régimen de 100 µL por minuto durante un período de 5 minutos.

La administración de una sustancia hidrofóbica a la dermis se usa para indicar que la sustancia se deposita de tal forma, que la sustancia

llega fácilmente a la dermis papilar altamente vascularizada y se absorbe rápidamente en los capilares sanguíneos y/o vasos linfáticos para estar sistémicamente biodisponible. Esto puede resultar de la colocación de la sustancia en la región superior de la dermis, es decir, la dermis papilar o en la porción superior de la dermis reticular relativamente menos vascular, de modo que la sustancia se difunde fácilmente en la dermis papilar.

La piel de los mamíferos contiene dos capas, como se describió anteriormente, específicamente, la epidermis y dermis. La epidermis se forma de hasta cinco capas, el estrato córneo, el estrato lúcido, el estrato granuloso, el estrato espinoso y el estrato germinativo, y la dermis se forma de dos capas, la dermis papilar superior y la dermis reticular más profunda. El grosor de la dermis y epidermis en los humanos varía de individuo a individuo y dentro de un individuo, en diferentes sitios del cuerpo. Por ejemplo, se ha reportado que la epidermis varía en espesor de alrededor de 40 a aproximadamente 90 µm, y que la dermis varía en espesor que varía desde apenas abajo de la epidermis, hasta una profundidad de menos de 1 mm en algunas regiones del cuerpo, hasta apenas bajo 2 a aproximadamente 4 mm en otras regiones del cuerpo, dependiendo del reporte de estudio particular (Hwang et al., *Ann Plastic Surg 46*:327-331, 2001; Southwood, *Plast. Reconstr. Surg 15*:423-429, 1955; Rushmer et al., *Science 154*:343-348, 1966). La invención de la presente con respecto a la administración a humanos, abarca la liberación de sustancias hacia la dermis en cualquier sitio deseado del cuerpo. De esta manera, la profundidad de colocación de la

sustancia dependerá de la profundidad de la dermis en el sitio deseado. Dicha colocación puede ser, por ejemplo, de hasta alrededor de 1 mm en ciertos casos para piel abdominal (Hwang et al., citado anteriormente), o hasta aproximadamente 4 mm en ciertos casos para piel de la espalda (Rushmer et al., citado anteriormente).

Para la mayoría de las áreas de la piel humana, se prefiere que una sustancia sea colocada predominantemente a una profundidad de por lo menos alrededor de 0.3 mm, más preferiblemente, por lo menos alrededor de 0.4 mm, y muy preferiblemente por lo menos alrededor de 0.5 mm, hasta una profundidad no mayor de aproximadamente 2.5 mm, más preferiblemente, no mayor de alrededor de 2.0 mm, y muy preferiblemente no mayor de alrededor de 1.7 mm, y esto dará como resultado absorción rápida de sustancias macromoleculares y/o hidrofóbicas. Se piensa que la colocación de la sustancia predominantemente a profundidades mayores y/o en la porción inferior de la dermis reticular, hace que la sustancia sea absorbida lentamente en la dermis reticular menos vascular o en la región subcutánea, lo cual daría como resultado absorción reducida de sustancias macromoleculares y/o hidrofóbicas. La liberación controlada de una sustancia hacia la dermis bajo la dermis papilar en la dermis reticular, pero suficientemente arriba de la interfaz entre la dermis y el tejido subcutáneo, debe permitir una migración eficiente (hacia fuera) de la sustancia hacia el lecho microcapilar vascular y linfático (no perturbado) (en la dermis papilar), en donde la sustancia puede ser absorbida en la circulación sistémica mediante estos microcapilares sin ser secuestrada

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en su trayecto por cualquier otro compartimento de tejido cutáneo.

La presente invención provee un método para tratamiento terapéutico mediante el suministro de un fármaco hidrofóbico u otra sustancia a un sujeto humano o animal no humano mediante elección directa hacia la dermis, en donde el fármaco o sustancia se administra mediante uno de una variedad de dispositivos de acceso dérmico. Se ha encontrado que las sustancias administradas de acuerdo a los métodos de la invención, exhiben parámetros farmacocinéticos mejorados y más clínicamente deseables, que los observados para la misma sustancia administrada mediante inyección subcutánea, es decir, mediante administración subcutánea de bolo.

El dispositivo de microporación o dispositivo de acceso dérmico usado para administración hacia la dermis de conformidad con la invención, no es crítico en tanto penetre la piel de un sujeto hasta la profundidad objetivo deseada hacia la dermis, sin pasar a través de la dermis hacia el tejido subcutáneo. En la mayoría de los casos, el dispositivo penetrará la piel y hasta una profundidad de aproximadamente 0.5-2 mm. Los medios de acceso dérmico pueden comprender agujas para inyección, catéteres o microagujas convencionales de todos los tipos conocidos, usados individualmente o en disposiciones de agujas múltiples. Los medios de acceso dérmico pueden comprender dispositivos sin aguja, incluyendo dispositivos de inyección balística. Los términos "agua" y "agujas", como se usan en la presente, se usan para abarcar dichas estructuras tipo aguja. El término microagujas, como se usa en la presente, se usa para abarcar estructuras de calibre menor de

aproximadamente 30, típicamente calibre de alrededor de 31 a 50 cuando dichas estructuras son de naturaleza cilíndrica. Las estructuras no cilíndricas abarcadas por el término microagujas serían por lo tanto de diámetro comparable, e incluyen las formas piramidal, rectangular, octagonal, acuñada y otras formas geométricas.

Los dispositivos de microporación o de acceso dérmico incluyen también dispositivos balísticos de inyección de fluidos, dispositivos de liberación de chorro de polvo, dispositivos de liberación piezoeléctricos, electromotrices o electromagnéticos asistidos, dispositivos de liberación asistidos por gas, los cuales penetran directamente la piel para proveer acceso para liberación o para liberar directamente sustancias hacia el sitio elegido dentro del espacio dérmico. La profundidad elegida de la liberación de sustancias por los medios de acceso dérmico puede ser controlada manualmente por el médico general, o con o sin la ayuda de medios indicadores que indican cuándo se alcanza la profundidad deseada. Sin embargo, de preferencia, el dispositivo tiene medios estructurales que controlan la penetración en la piel hasta la profundidad deseada dentro de la dermis. Esto se logra más típicamente mediante un área o cubo ensanchado asociado con el eje de los medios de acceso dérmico que pueden tomar la forma de una estructura o plataforma de refuerzo a la cual están unidas las agujas. La longitud de las microagujas como medios de acceso dérmico es, de preferencia, menor de 2 mm. Pueden usarse en la invención como microagujas individuales, o en un ensamble de microagujas múltiples en

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disposiciones lineales o bidimensionales para incrementar la velocidad de liberación, o la cantidad de sustancia liberada en un período determinado. Las microagujas pueden incorporarse en una variedad de dispositivos tales como soportes y alojamientos que pueden servir también para limitar la profundidad de penetración. Los dispositivos de acceso dérmico de la invención pueden incorporar también depósitos que contengan la sustancia antes de la liberación, o bombas u otros medios para liberar el fármaco u otra sustancia bajo presión. En forma alternativa, el dispositivo que aloja a los dispositivos de acceso dérmico puede unirse externamente a dichos componentes adicionales.

Las microagujas adecuadas para administración a la dermis pueden tener, por ejemplo, las dimensiones de alrededor de 250 micras de diámetro exterior, y menos de 2 mm de longitud expuesta. Las microagujas pueden construirse de acero, otros metales tales como cobre, níquel, titanio, o mezclas de los mismos, silicio, cerámica, plástico, o cualquier material adecuado, o combinaciones de los mismos.

La farmacocinética de tipo intravenoso se logra administrando una sustancia a la dermis en contacto íntimo con la microvasculatura capilar y microvasculatura linfática de la dermis capilar. Deberá entenderse que los términos microcapilares o lechos capilares de la dermis, se usan para referirse a vías de drenaje vascular o linfático dentro de la dermis.

Sin pretender que sea limitado por algún mecanismo de acción teórico, se piensa que la absorción rápida observada después de la

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administración en la dermis, se logra como resultado de los plexos ricos de vasos linfáticos y sanguíneos en la dermis. Sin embargo, no se espera por sí misma que la presencia de sangre y plexos linfáticos en la dermis dé una absorción mejorada de sustancias hidrofóbicas, ya que las sustancias tienden a separarse en compartimentos lipofílicos en una forma de depósito para disminuir de esta manera su disponibilidad para absorción. Sin embargo, la absorción mejorada observada tras la administración de una sustancia hidrofóbica hacia la dermis puede resultar de la falta de adipocitos y, por lo tanto, la falta sustancial de compartimentos lipofílicos en la dermis. Otra contribución posible a la absorción mejorada inesperada lograda después de la liberación de sustancias hidrofóbicas hacia la dermis, puede resultar de un incremento en el flujo sanguíneo y la permeabilidad capilar causada por la inyección en la dermis. Por ejemplo, se sabe que la realización de un pinchazo a una profundidad de 3 mm produce un incremento en el flujo sanguíneo, y se ha postulado que esto es independiente del estímulo doloroso y se debe a la liberación de histamina por el tejido (Arildsson et al., *Microvascular Res. 59*:122-130, 2000). Esto es también consistente con la observación de que una respuesta inflamatoria aguda inducida en respuesta a lesión de la piel, produce un incremento transitorio en el flujo sanguíneo y permeabilidad capilar (véase *Physiology, Biochemistry, and Molecular Biology of the Skin*, segunda edición, L. A. Goldsmith, ed., Oxford Univ. Press, New York, 1991, p. 1060; Wilhem, *Rev. Can. Biol. 30*:153-172, 1971). Al mismo tiempo, se esperaría que la inyección en la dermis aumente la presión

intersticial. Se sabe que el aumento de la presión intersticial desde valores a partir de un valor normal de alrededor de 7 mm de Hg a aproximadamente +2 mm de Hg, distiende los vasos linfáticos y aumenta el flujo de linfa (Skobe et al., *J. Investig. Dermatol. Symp. Proc.* 5:14-19, 2000). De esta manera, se piensa que la presión intersticial incrementada inducida por inyección en la dermis induce flujo de linfa incrementado y absorción incrementada de sustancias inyectadas en la dermis.

Los métodos de administración útiles para llevar a cabo la invención, incluyen liberación por infusión y bolo de fármacos y otras sustancias en sujetos humanos o animales. Una dosis de bolo es una dosis individual liberada en un volumen unitario individual durante un período relativamente breve, típicamente de alrededor de 10 minutos o menos, más preferiblemente de alrededor de 2 minutos o menos. La administración mediante administración de bolo puede llevarse a cabo mediante el uso de un dispositivo adecuado para dar acceso a la dermis, el cual contiene también un mecanismo para impulsar la sustancia en la dermis tal como, por ejemplo, una aguja o microaguja acoplada a una jeringa accionada por una bomba. En forma alternativa, la liberación por aguja y jeringa puede realizarse manualmente por empuje, mientras se monitorea el tiempo de inyección, típicamente alrededor de 2 minutos o menos, con el segundero de un reloj.

La administración por infusión comprende administrar un fluido a un régimen seleccionado que puede ser constante o variable, durante un período relativamente más extendido, típicamente mayor de alrededor de 10

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mm. Para liberar una sustancia, el dispositivo de acceso dérmico se coloca adyacente a la piel de un sujeto, proveyendo directamente el acceso elegido dentro de la dermis, y la sustancia o las sustancias son liberadas o administradas en la dermis, en donde pueden actuar localmente o ser absorbidas en la corriente sanguínea, y ser distribuidas sistemáticamente. El dispositivo de acceso dérmico puede conectarse a un depósito que contiene a la sustancia o las sustancias que serán liberadas. La liberación desde el depósito en la dermis puede ocurrir pasivamente, sin la aplicación de presión externa u otros medios de accionamiento sobre la sustancia o las sustancias que serán liberadas, y/o activamente, con la aplicación de presión u otro método de accionamiento. Ejemplos de dispositivos preferidos que generan presión incluyen bombas, jeringas, membranas elastoméricas, presión gaseosa, bombeo piezoeléctrico, electromotriz o electromagnético, arandelas o resortes de Belleville, o combinaciones de los mismos. Si se desea, la velocidad de liberación de la sustancia puede controlarse en forma variable mediante medios que generen presión. Como resultado, la sustancia entra a la dermis y es absorbida en una cantidad y a una velocidad suficiente para producir un resultado clínicamente eficaz. El término resultado clínicamente eficaz, como se refiere en la presente, se usa para incluir respuestas útiles desde el punto de vista terapéutico y de diagnóstico que resultan de la administración de una sustancia o sustancias.

Las sustancias hidrofóbicas de la presente invención están en una formulación adecuada para administración a la dermis. La sustancia

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hidrofóbica puede estar en forma de una solución en un vehículo no acuoso o un vehículo que sea una mezcla de agua y un cosolvente. Vehículos y/o cosolventes no acuosos incluyen azúcares y polímeros hidrofílicos de alto peso molecular (véase, por ejemplo, Yalkowsky, *Solubility and Solubilization in Aqueous Media*, Oxford University Press, New York, 1999). Ejemplos no limitativos de dichos cosolventes incluyen etanol, propilenglicol, glicerina, sorbitol, polietilenglicol 400, polietilenglicol 4000, poloxámero 188, carbonato de propileno, polivinilpirrolidona, dimetilisosorbida, N-metilpirrolidona, y combinaciones de los mismos. Entre dichas formulaciones, el vehículo para la sustancia hidrofóbica contendrá por lo menos un cosolvente a una concentración de alrededor de 5% a aproximadamente 95% sobre una base de peso/peso. Las formulaciones preferidas contendrán por lo menos un cosolvente a una concentración de por lo menos alrededor de 10%, por lo menos aproximadamente 20%, por lo menos alrededor de 30%, por lo menos aproximadamente 40%, hasta alrededor de 50% o más en un medio acuoso, sobre una base de peso/peso. Pueden usarse también mezclas de cosolventes.

Pueden estar también presentes agentes tensioactivos en la formulación como agentes de solubilización. Dichos agentes tensioactivos pueden ser aniónicos, catiónicos, zwitteriónicos o no iónicos (véase, por ejemplo, Yalkowisky, citado anteriormente, pp. 236-320). Ejemplos no limitativos de agentes tensioactivos adecuados incluyen fosfolípidos tales como lecitina, cloruro de benzalconio, cloruro de bencetonio, cloruro de

cetilpiridinio, dioctil sulfosuccinato de sodio, nonoxinol 9, nonoxinol 10, octoxinol 9, poloxámeros, polioxietileno (8), monoglicéridos y diglicéridos caprílicos/cápricos (por ejemplo, Labrasol™ de Gattefossé), aceite de ricino de polioxietileno (35), éter cetoestearílico de polioxietileno (20), aceite de ricino hidrogenado de polioxietileno (40), éster oleílico de polioxietileno (10), estearato de polioxietileno (40), polisorbato 20, polisorbato 40, polisorbato 60, polisorbato 80 (por ejemplo, Tween™ 80 de ICI), laurato de propilenglicol (por ejemplo, Lauroglycol™ de Gattefossé), lauril sulfato de sodio, monolaurato de sorbitán, monooleato de sorbitán, monopalmitato de sorbitán, monoestearato de sorbitán, tiloxapol, y mezclas de los mismos.

Las formulaciones que contienen agentes tensioactivos comprenden, de preferencia, de alrededor de 1% o menos hasta aproximadamente 15% de agente tensioactivo, sobre una base de peso/peso. Las concentraciones preferidas de agente tensioactivo son de por lo menos aproximadamente 2%, por lo menos alrededor de 3%, por lo menos aproximadamente 4%, hasta alrededor de 5%, sobre una base de peso/peso.

La sustancia hidrofóbica puede estar también en forma de nanopartículas o nanocristales dispersados o suspendidos en un medio acuoso. En dicha formulación, la sustancia hidrofóbica está en nanopartículas, es decir, teniendo una de D_{90} menor de aproximadamente 1 μm (siendo D_{90} un diámetro tal que 90% en peso de las partículas son más pequeñas que este diámetro en su dimensión más larga). En dichas formulaciones de nanopartículas, el tamaño de partícula promedio en peso es típicamente de

alrededor de 100 nm a aproximadamente 800 nm, por ejemplo, de alrededor de 150 nm a aproximadamente 600 nm, o de alrededor de 200 nm a aproximadamente 400 nm. Las nanopartículas pueden tener también un tamaño de partícula D_{25} de alrededor de 450 nm a aproximadamente 1000 nm, y más preferiblemente de alrededor de 500 nm a aproximadamente 900 nm (siendo D_{25} un diámetro tal que 25% en peso de las partículas son más pequeñas que este diámetro en su dimensión más larga). Composiciones farmacéuticas que comprendan cualquiera de dichas formulaciones de nanopartículas de la sustancia hidrofóbica, pueden ser útiles en los métodos de la presente invención.

Se conocen numerosos procedimientos para la preparación de composiciones de nanopartículas de agentes terapéuticos. Algunos de estos procedimientos usan medios mecánicos, tales como molienda, para reducir el tamaño de partícula a una nanoescala, y otros precipitan nanopartículas a partir de una solución. Procedimientos ilustrativos se describen en las publicaciones de patente citadas a continuación:

Patente de E.U.A. No. 4,826,689 a Violanto & Fischer.

Patente de E.U.A. No. 5,145,684 a Liversidge *et al.*

Patente de E.U.A. No. 5,298,262 a Na & Rajagopalan.

Patente de E.U.A. No. 5,302,401 a Liversidge *et al.*

Patente de E.U.A. No. 5,336,507 a Na & Rajagopalan.

Patente de E.U.A. No. 5,340,564 a Illig & Sarpotdar.

Patente de E.U.A. No. 5,346,702 a Na & Rajagopalan.

Patente de E.U.A. No. 5,352,459 a Hollister *et al.*

Patente de E.U.A. No. 5,354,560 a Lovrecich.

Patente de E.U.A. No. 5,384,124 a Courteille *et al.*

Patente de E.U.A. No. 5,429,824 a June.

Patente de E.U.A. No. 5,503,723 a Ruddy *et al.*

Patente de E.U.A. No. 5,510,118 a Bosch *et al.*

Patente de E.U.A. No. 5,518,187 a Bruno *et al.*

Patente de E.U.A. No. 5,518,738 a Eickhoff *et al.*

Patente de E.U.A. No. 5,534,270 a De Castro.

Patente de E.U.A. No. 5,536,508 a Canal *et al.*

Patente de E.U.A. No. 5,552,160 a Liversidge *et al.*

Patente de E.U.A. No. 5,560,931 a Eickhoff *et al.*

Patente de E.U.A. No. 5,560,932 a Bagchi *et al.*

Patente de E.U.A. No. 5,565,188 a Wong *et al.*

Patente de E.U.A. No. 5,569,448 a Wong *et al.*

Patente de E.U.A. No. 5,571,536 a Eickhoff *et al.*

Patente de E.U.A. No. 5,573,783 a Desieno & Stetsko.

Patente de E.U.A. No. 5,580,579 a Ruddy *et al.*

Patente de E.U.A. No. 5,585,108 a Ruddy *et al.*

Patente de E.U.A. No. 5,587,143 a Wong.

Patente de E.U.A. No. 5,591,456 a Franson *et al.*

Patente de E.U.A. No. 5,622,938 a Wong.

Patente de E.U.A. No. 5,662,883 a Bagchi *et al.*

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Patente de E.U.A. No. 5,665,331 a Bagchi *et al.*

Patente de E.U.A. No. 5,718,919 a Ruddy *et al.*

Patente de E.U.A. No. 5,747,001 a Wiedmann *et al.*

Publicación de patente internacional No. WO 93/25190.

Publicación de patente internacional No. WO 96/24336.

Publicación de patente internacional No. WO 97/14407.

Publicación de patente internacional No. WO 98/35666.

Publicación de patente internacional No. WO 99/65469.

Publicación de patente internacional No. WO 00/18374.

Publicación de patente internacional No. WO 00/27369.

Publicación de patente internacional No. WO 00/30615.

Los expertos en la técnica adaptarán fácilmente los procedimientos de la presente descritos, a la preparación de la sustancia hidrofóbica en forma de nanopartículas.

Ejemplos ilustrativos se describen a continuación:

EJEMPLO 1

Este ejemplo ilustra la absorción sistémica mejorada de (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona tras administración a la dermis.

El compuesto (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona tiene un valor logP calculado de 1.62 usando el

programa logKow (Syracuse Research Corporation, North Syracuse, NY 13212; véase también Meylan y Howard, citado anteriormente). De conformidad con la invención de la presente, se muestra que este compuesto da mayores niveles en plasma y parámetros farmacocinéticos mejorados tras su administración a la dermis, que los que se obtienen tras la administración subcutánea.

Se usaron seis cerdos enanos de Yucatán que pesaban 20-25 kg. Se prepararon soluciones de (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona a concentraciones de 10 mg/mL a pH 5.5 en regulador de pH de citrato/fosfato con dextrosa suficiente, para lograr isotonicidad. Se recibió (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona mediante las siguientes vías: (A) bolo intravenoso, (B) inyección subcutánea, y (C) inyección a la dermis mediante una disposición de microagujas. Se usó un total de seis animales en un diseño de intersección completo, en donde cada animal recibió una dosis de 1.0 mg mediante todas las vías de administración en un volumen de inyección de 0.1 mL.

La dosis intravenosa se administró mediante un catéter en la vena de la oreja. La liberación subcutánea fue a través de una aguja normal de 1.27 cm, calibre 30. La liberación hacia la dermis fue a través de una disposición de microagujas de tres puntos que tenía tres agujas calibre 34 con separación de 7 mm y profundidad de 1 mm hacia el flanco derecho del animal entre la caja torácica y la pata trasera. La administración subcutánea e intravenosa fue mediante inyección manual. La administración hacia la dermis

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fue a un régimen de 90 µL/min mediante la bomba de una jeringa.

El diseño de estudio fue una intersección completa, en donde cada animal recibió administración intravenosa, subcutánea y dérmica. Cada animal recibió tres tratamientos durante un período de dos semanas, con un período de descanso mínimo de 2 días entre las dosis subsecuentes. La dosificación fue de acuerdo al programa mostrado a continuación en el cuadro 2:

CUADRO 2

Programa de dosificación*

Animal	Semana 1		Semana 2		Semana 3		Semana 4		Semana 5
	Dosis 1	Dosis 2	Dosis 3	Dosis 4	Dosis 5	Dosis 6	Dosis 7	Dosis 8	Dosis 9
1	IV	ID	SC						
2	ID	SC	IV						
3				SC	IV	ID			
4				IV	ID	SC			
5							ID	SC	IV
6							SC	IC	ID

*IV representa administración intravenosa, SC representa administración subcutánea, e ID representa administración hacia la dermis.

Se obtuvieron muestras de sangre del orificio de acceso de la vena cava poco antes de la dosificación y a 5, 10, 15, 20, 30, 45, 60 minutos y 2, 3, 4, 6, 8, 10, 14 y 24 horas después de la administración. El registro del tiempo se inició al cese de la inyección mediante un método determinado. Se

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colectaron muestras de sangre venosa en tubos Vacutainer que contenían EDTA, centrifugados a aproximadamente 1000 g durante 10 minutos a 4°C. Después de la centrifugación, la capa de plasma se transfirió a recipientes de plástico de almacenamiento, y se almacenó congelada a -70°C hasta la realización de la prueba.

La prueba de las muestras de plasma de los cerdos se llevó a cabo mediante análisis de CLAR. Los resultados se muestran a continuación en el cuadro 3:

CUADRO 3

Concentraciones en plasma (ng/mL) de (*R*)-5,6-dihidro-5-(metilamino)-4H-Imidazo[4,5-*f*]-quinolino-2(1H)-tiona después de administración mediante varias vías en cerdos enanos de Yucatán

Tiempo	IV		ID		SC	
	Media	SD	Media	SD	Media	SD
5 min	29.8	7.0	24.8	12.4	10.0	2.2
10 min	20.5	4.5	22.5	9.0	15.3	3.0
15 min	18.5	4.2	16.4	6.2	16.0	1.7
20 min	15.3	2.2	18.0	6.6	14.5	1.8
30 min	13.1	2.4	14.0	2.4	14.0	0.9
45 min	10.7	2.3	9.9	2.7	9.9	3.1
1 hr	9.1	1.5	9.0	1.6	8.9	1.4
2 hr	6.7	1.4	5.7	1.9	5.6	1.4
3 hr	2.8	2.6	4.2	1.5	4.1	2.0
4 hr	1.6	1.5	3.6	1.4	2.2	1.9
6 hr	2.6	4.1	0.4	1.0	1.6	3.3
8 hr	0	0	0	0	0.6	1.6
10 hr	0	0	0	0	0	0
14 hr	0	0	0	0	0	0
24 hr	0	0	0	0	0	0

El fármaco se administró mediante administración intravenosa (IV), administración subcutánea (SC), y mediante administración hacia la dermis (ID). La dosis intravenosa se administró al subgrupo de dosificación de 1.0 mg en una vena de la oreja.

Como se muestra en el cuadro 3, la administración en la dermis tendió a producir mayores niveles de fármaco en plasma que los que se obtienen después de la administración subcutánea. El análisis de los datos mediante análisis de heterogeneidad de regresión, reveló que los valores obtenidos después de la administración a la dermis y la administración intravenosa, no fueron diferentes entre sí, pero sí diferentes de valores obtenidos después de la administración subcutánea.

Los parámetros farmacocinéticos se calcularon usando el sistema del Watson Drug Metabolism Laboratory Information Management, versión 6.2.0.02 (Innaphase Corp., Filadelfia, PA). Los parámetros determinados fueron los de concentración máxima en plasma, $C_{máx}$, tiempo a la concentración máxima en plasma, $T_{máx}$, área bajo la curva calculada a t – infinito, $T_{máx}$, y vida media para disminución en la concentración en plasma, $T_{1/2}$.

Los parámetros farmacocinéticos se muestran en el cuadro 4 siguiente:

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CUADRO 4

Parámetros farmacocinéticos medios (± desviación estándar) de (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona después de administración mediante varias vías en cerdos enanos de Yucatán

Parámetro	Dosis de 1.0 mg		
	IV (n=6)	ID (n=6)	SC (n=6)
Dosis (μg/kg)	40.9 (3.2)	41.3 (3.9)	40.3 (3.4)
$C_{máx}$ (ng/mL)	29.8 (7.0)	26.7 (10.2)	16.9 (2.6)
$T_{máx}$ (hr)	0.083 (0.000)	0.139 (0.101)	0.222 (0.068)
$AUC_{(0-\infty)}$ (ng*hr/mL)	32.4 (8.2)	33.6 (9.0)	32.1 (9.2)
$T_{1/2}$ (hr)	1.45 (0.38)	1.61 (0.70)	1.5 (0.53)

El fármaco se administró mediante administración intravenosa (IV), administración subcutánea (SC), y mediante administración hacia la dermis (ID).

Como se muestra en el cuadro anterior, los valores de $C_{máx}$ fueron consistentemente mayores, y los valores de $T_{máx}$ fueron consistentemente menores después de administración hacia la dermis que los valores para los mismos parámetros obtenidos después de la administración subcutánea de la sustancia hidrofóbica, (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2(1H)-tiona.

Puesto que pueden hacerse varios cambios en los métodos y

composiciones anteriores sin apartarse del alcance de la invención, se pretende que toda la materia contenida en la descripción anterior sea interpretada como ilustrativa y no en un sentido limitativo.

Todas las referencias citadas en esta especificación se incorporan en la presente como referencia. Se pretende que la inclusión de las referencias en la presente resuma sólo las aseveraciones hechas por los autores, y no se haga mención alguna de que alguna referencia constituye técnica anterior relevante a la patentabilidad. El solicitante se reserva el derecho de desafiar la exactitud y pertinencia de las referencias citadas.

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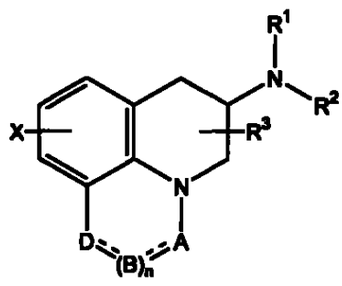
NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- Un método para la administración sistémica de un agonista de dopamina hidrofóbico a un mamífero, el método caracterizado porque comprende liberar el agonista de dopamina a la dermis del mamífero, en donde se produce absorción sistémica incrementada en comparación con la absorción producida tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

2.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-

metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3, y n es 0 ´0 1; y D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde —— es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH, SO_2; entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH, SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3; entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N; entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, y B es CH o N; entonces D es CH o N; y sales farmacéuticamente aceptables del mismo al humano.

3.- El método de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-tiona, o una sal

farmacéuticamente aceptable del mismo.

4.- El método de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona o una sal farmacéuticamente aceptable del mismo.

5.- El método de conformidad con la reivindicación 1, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

6.- El método de conformidad con la reivindicación 5, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

7.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina hidrofóbica se libera a la dermis mediante inyección de bolo.

8.- El método de conformidad con la reivindicación 7, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

9.- El método de conformidad con la reivindicación 8, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 2 minutos.

10.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

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11.- El método de conformidad con la reivindicación 1, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

12.- El método de conformidad con la reivindicación 11, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

13.- El método de conformidad con la reivindicación 10, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

14.- El método de conformidad con la reivindicación 10, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

15.- El método de conformidad con la reivindicación 10, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

16.- El método de conformidad con la reivindicación 1, caracterizado además porque la liberación es a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o ballstica de gases.

17.- El método de conformidad con la reivindicación 16, caracterizado además porque la liberación es a través de por lo menos una

aguja hueca.

18.- El método de conformidad con la reivindicación 1, caracterizado además porque la aguja hueca (por lo menos una) comprende una disposición de microagujas.

19.- El método de conformidad con la reivindicación 18, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

20.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 1.5 o más.

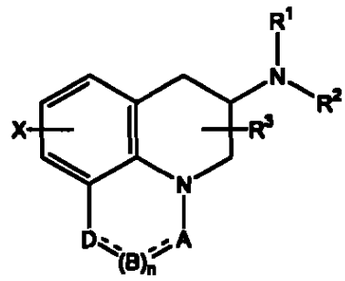
21.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

22.- Un método para la administración de un agonista de dopamina hidrofóbico a un mamífero, el método caracterizado porque comprende liberar selectivamente el agonista de dopamina a la dermis del mamífero para lograr absorción sistémica del agonista de dopamina a partir de la dermis.

23.- El método de conformidad con la reivindicación 22, caracterizado además porque la absorción sistémica incrementada del agonista de dopamina se produce tras liberar el agonista de dopamina a la dermis en comparación con la absorción producida tras liberar el agonista de

dopamina subcutáneamente mediante inyección de bolo.

24.- El método de conformidad con la reivindicación 23, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3, y n es 0 ´0 1; y D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ═══ es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH, SO_2; entonces D es CH_2, CH-(halógeno), en donde

halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH, SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3; entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N; entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, y B es CH o N; entonces D es CH o N; y sales farmacéuticamente aceptables del mismo al humano.

25.- El método de conformidad con la reivindicación 24, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

26.- El método de conformidad con la reivindicación 24, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona o una sal farmacéuticamente aceptable del mismo.

27.- El método de conformidad con la reivindicación 23, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

28.- El método de conformidad con la reivindicación 27,

caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

29.- El método de conformidad con la reivindicación 23, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo.

30.- El método de conformidad con la reivindicación 29, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

31.- El método de conformidad con la reivindicación 30, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 2 minutos.

32.- El método de conformidad con la reivindicación 23, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

33.- El método de conformidad con la reivindicación 23, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

34.- El método de conformidad con la reivindicación 33, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

35.- El método de conformidad con la reivindicación 32,

caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

36.- El método de conformidad con la reivindicación 32, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

37.- El método de conformidad con la reivindicación 32, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

38.- El método de conformidad con la reivindicación 23, caracterizado además porque la liberación es a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

39.- El método de conformidad con la reivindicación 38, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

40.- El método de conformidad con la reivindicación 23, caracterizado además porque por lo menos una aguja hueca comprende una disposición de microagujas.

41.- El método de conformidad con la reivindicación 40, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

42.- El método de conformidad con la reivindicación 23,

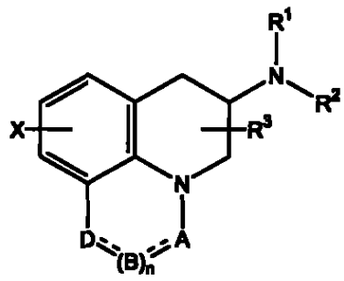
caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 1.5 o más.

43.- El método de conformidad con la reivindicación 23, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

44.- Un método para la administración de un agonista de dopamina hidrofóbico a un mamífero, el método comprende liberar selectivamente el agonista de dopamina a la dermis del mamífero, en donde se obtiene absorción sistémica del agonista de dopamina a partir de la dermis.

45.- El método de conformidad con la reivindicación 42, caracterizado además porque la absorción sistémica incrementada del agonista de dopamina se produce tras liberar el agonista de dopamina a la dermis en comparación con la absorción producida tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

46.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; y n es 0 ó 1; y D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ⎯⎯ es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o $N\text{-}CH_3$; (2) cuando n es 0 y A es CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N, entonces D es CH, N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH, SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH, $N\text{-}CH_3$, entonces D es CH_2, C=O, O, NH, $N\text{-}CH_3$; (4) cuando n es 1 y A es CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N; y B es CH, N, entonces D es CH_2, C=O, O, NH, $N\text{-}CH_3$; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, y B es CH o N, entonces

D es CH, N; y sales farmacéuticamente aceptables del mismo, al humano.

47.- El método de conformidad con la reivindicación 44, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

48.- El método de conformidad con la reivindicación 44, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona, o una sal farmacéuticamente aceptable del mismo.

49.- El método de conformidad con la reivindicación 43, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

50.- El método de conformidad con la reivindicación 47, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

51.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo.

52.- El método de conformidad con la reivindicación 49, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

53.- El método de conformidad con la reivindicación 50, caracterizado además porque el agonista de dopamina hidrofóbico se libera a

la dermis en no más de 2 minutos.

54.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

55.- El método de conformidad con la reivindicación 43, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

56.- El método de conformidad con la reivindicación 53, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

57.- El método de conformidad con la reivindicación 52, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

58.- El método de conformidad con la reivindicación 52, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

59.- El método de conformidad con la reivindicación 52, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

60.- El método de conformidad con la reivindicación 43, caracterizado además porque la liberación es a través de un microporo

cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

61.- El método de conformidad con la reivindicación 58, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

62.- El método de conformidad con la reivindicación 43, caracterizado además porque al menos una aguja hueca comprende una disposición de microagujas.

63.- El método de conformidad con la reivindicación 60, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

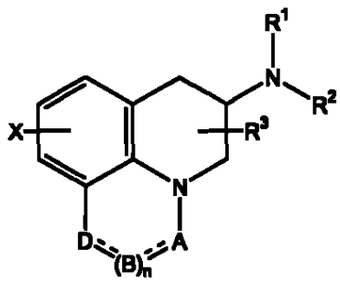
64.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 1.5 o más.

65.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

66.- Un método para la administración de un agonista de dopamina hidrofóbico a un mamífero, el método comprende liberar selectivamente el agonista de dopamina a la dermis del mamífero, para lograr una biodisponibilidad sustancialmente mayor y/o una $C_{máx}$ sustancialmente mayor y/o un $T_{máx}$ sustancialmente más corto y/o un T_{lag} sustancialmente más

corto y/o un pKa sustancialmente mayor, en comparación con los que se obtienen tras la administración subcutánea de bolo del agonista de dopamina a una dosis idéntica.

67.- El método de conformidad con la reivindicación 64, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; y n es 0 ó 1; y D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ⎯⎯ es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-

(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o $N\text{-}CH_3$; (2) cuando n es 0 y A es CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o $N\text{-}CH_3$, entonces D es CH_2, C=O, O, NH o $N\text{-}CH_3$; (4) cuando n es 1 y A es CH_2, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N; y B es CH o N, entonces D es CH_2, C=O, O, NH o $N\text{-}CH_3$; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo, al humano.

68.- El método de conformidad con la reivindicación 65, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

69.- El método de conformidad con la reivindicación 65, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona, o una sal farmacéuticamente aceptable del mismo.

70.- El método de conformidad con la reivindicación 64, caracterizado además porque la inyección subcutánea de bolo se libera en no

más de 10 minutos.

71.- El método de conformidad con la reivindicación 68, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

72.- El método de conformidad con la reivindicación 64, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo.

73.- El método de conformidad con la reivindicación 70, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

74.- El método de conformidad con la reivindicación 71, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 2 minutos.

75.- El método de conformidad con la reivindicación 64, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

76.- El método de conformidad con la reivindicación 64, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

77.- El método de conformidad con la reivindicación 74, caracterizado además porque el parámetro farmacocinético mejorado

comprende biodisponibilidad incrementada del agonista de dopamina.

78.- El método de conformidad con la reivindicación 73, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

79.- El método de conformidad con la reivindicación 73, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

80.- El método de conformidad con la reivindicación 73, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

81.- El método de conformidad con la reivindicación 64, caracterizado además porque la liberación es a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

82.- El método de conformidad con la reivindicación 79, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

83.- El método de conformidad con la reivindicación 64, caracterizado además porque la aguja hueca comprende una disposición de microagujas.

84.- El método de conformidad con la reivindicación 81, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba

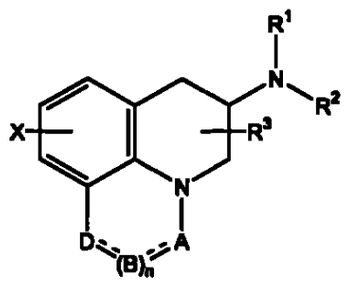
electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

85.- El método de conformidad con la reivindicación 64, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 1.5 o más.

86.- El método de conformidad con la reivindicación 64, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

87.- Un método para la administración de un agonista de dopamina hidrofóbico a un mamífero, el método comprende liberar selectivamente el agonista de dopamina a la dermis del mamífero, en donde se logra una biodisponibilidad sustancialmente mayor y/o una $C_{máx}$ sustancialmente mayor y/o un $T_{máx}$ sustancialmente más corto y/o un T_{lag} sustancialmente más corto y/o un K_a sustancialmente mayor, en comparación con los que se obtienen después de la administración subcutánea de bolo del agonista de dopamina a una dosis idéntica.

88.- El método de conformidad con la reivindicación 85, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; y n es 0 o 1; y D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ⎯⎯ es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH, SO_2; entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH, N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; entonces D es CH, N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH, SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH, N-CH_3; entonces D es CH_2, C=O, O, NH, N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; y B es CH, N; entonces D es CH_2, C=O, O, NH, N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, y B es CH, N; entonces D

es CH, N; y sales farmacéuticamente aceptables del mismo, al humano.

89.- El método de conformidad con la reivindicación 86, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

90.- El método de conformidad con la reivindicación 86, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona,, o una sal farmacéuticamente aceptable del mismo.

91.- El método de conformidad con la reivindicación 85, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

92.- El método de conformidad con la reivindicación 89, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

93.- El método de conformidad con la reivindicación 85, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo.

94.- El método de conformidad con la reivindicación 91, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

95.- El método de conformidad con la reivindicación 92, caracterizado además porque el agonista de dopamina hidrofóbico se libera a

la dermis en no más de 2 minutos.

96.- El método de conformidad con la reivindicación 85, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

97.- El método de conformidad con la reivindicación 85, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

98.- El método de conformidad con la reivindicación 95, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

99.- El método de conformidad con la reivindicación 94, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

100.- El método de conformidad con la reivindicación 94, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

101.- El método de conformidad con la reivindicación 94, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

102.- El método de conformidad con la reivindicación 85, caracterizado además porque la liberación es a través de un microporo

cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

103.- El método de conformidad con la reivindicación 85, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

104.- El método de conformidad con la reivindicación 85, caracterizado además porque la aguja hueca comprende una disposición de microagujas.

105.- El método de conformidad con la reivindicación 102, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

106.- El método de conformidad con la reivindicación 85, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 1.5 o más.

107.- El método de conformidad con la reivindicación 85, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

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RESUMEN DE LA INVENCION

Se describe un método para la administración sistémica de un agonista de dopamina hidrofóbico a un mamífero; el método consiste en liberar el agonista de dopamina hidrofóbico a la dermis del mamífero, con lo cual se logra absorción sistémica mejorada en comparación con la absorción producida tras liberar la sustancia subcutáneamente mediante administración de bolo.

MG

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6794S-000023POB
International Preliminary Exam Report

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Holland, Donald R.
HARNESS, DICKEY & PIERCE P.L.C.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
ETATS-UNIS D'AMERIQUE

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DEC 04 2003

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing (day/month/year)	01.12.2003
Applicant's or agent's file reference: 6794S-023POB	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/19918	24.06.2002	29.08.2001

Applicant
PHARMACIA CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purpose of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Rossi, C Tel. +31 70 340-3382

Form PCT/IPEA/416 (July 1992)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 67948-023POB	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/19918	International filing date (day/month/year) 24.06.2002	Priority date (day/month/year) 29.06.2001
International Patent Classification (IPC) or both national classification and IPC A61M5/158		
Applicant PHARMACIA CORPORATION		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 19 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.01.2003	01.12.2003
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Martin, E Telephone No. +31 70 340-2662

Form PCT/IPEA/409 (Cover Sheet) (January 1994)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US02/19918

I. Basis of the report

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

Description, Pages

1-32 as originally filed

Claims, Numbers

1-102 received on 22.09.2003 with letter of 19.09.2003

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

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

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT International application No. PCT/US02/19918

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-107 (all in part)

   because:

   ☒ the said international application, or the said claims Nos. 1-107, with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-107 (all in part) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-107
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-107
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1-107

2. Citations and explanations

   see separate sheet

Re Item I

The amendments filed with the letter dated 19-09-2003 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following: claims 1, 22 and 43.

The explanation of the applicant for the amendments of claims 1, 22 and 43 cannot be accepted, as paragraph 50, final sentence (page 23, lines 29-31) cannot function as the basis for the amendment of claims 1, 22 and 43. In paragraph 50 "increased absorption of substances injected into the dermis" is described. The subject-matter of claims 1, 22 and 43 differs from this in that "increased systemic absorption" is not described. The feature of increased systemic absorption of a hydrophobic dopamine agonist having a logP of 1.5 or greater after delivering the dopamine agonist by bolus injection to the dermis is not disclosed in the application as originally filed.

The following amendments are not contrary to Article 34(2)(b) PCT: claims 19, 21, 45, 63 and 83. The basis for "delivering the dopamine agonist by bolus injection to the dermis", "a hydrophobic dopamine agonist having a logP of about 1.5 or greater" and "a hydrophobic dopamine agonist having a logP of about 2.0 or greater" can be found in claims 1, 7, 20, 22, 29, 42, 44, 51, 64, 66, 72, 85 and paragraph 16 of the application as originally filed.

The examination is being carried out on claims 1-107 as filed on 01-04-2003.

Re Item III

1. Claims 1-107 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Claims 1-107 (all in part) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined.

2.1 Claims 1-107 attempt to define the subject-matter in terms of the result to be achieved, namely "improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection", or "selectively delivering the dopamine agonist to the dermis", or "a

substantially higher bioavailability and/or a substantially higher C_{max}, and/or a substantially higher T_{max}, and/or a substantially shorter T_{lag}, and/or a substantially greater K_a, as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose". These features do not provide instructions which are sufficiently clear for an expert to reduce them to practice without undue burden.

The description does not specify the experimental methods and conditions under which comparison with the bolus subcutaneous administration should be performed, furthermore no tests are specified by which the results of the comparison with the bolus subcutaneous administration, or the selective delivery to the dermis, can be verified directly and positively. The method of intradermal administration, the method of subcutaneous administration, the species, the subjects, the number of subjects, the experimental design of the studies, the assay methods, the conditions of the studies, and the method of calculation of parameters are not specified. For the parameters T_{max}, C_{max}, T_{lag}, it is not specified if they are determined in blood, plasma, urine or other body fluids. For the parameter of bioavailability it is not specified if relative or absolute bioavailability is meant. Moreover, the definition of the bioavailability given on page 7, paragraph 18 of the description is not according to the generally used definition, because the calculation is not based on the dosage and AUC (or clearance), of an intravenous dosis and an extravascular dosis, nor is the proviso made that the clearance should remain constant.

Moreover, it is clear from the description in paragraphs 20, 40-41 and 43 that the following features are essential to the definition of the invention:

(1) administration into the dermis and administration into the reference site such as subcutaneous tissue involve the same amount and concentration of drug as well as the same carrier vehicle;
(2) comparison between administration into the dermis and administration into the reference site such as subcutaneous tissue should be at the same rate of administration in terms of amount and volume per unit time;
(3) the depth of placement of the substance in the dermis should be at a depth of at least 0.3 mm up to a depth of no more than about 2.5 mm;
(4) T_{max} is a value representing the time to achieve maximal blood concentration of the compound;
(5) C_{max} is a value representing the maximum blood concentration of the

compound.

Since independent claims 1, 22, 44, 66 and 87 do not contain these features they do not meet the requirement following from Article 6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

Furthermore, the term "improved" used in claims 1, 11, 23, 33, 45, 55, 76 and 97 is vague and unclear. It is not clear whether the term "improved" means an increase or a decrease, or both. This term leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

The definitions of the parameters, the reference bolus subcutaneous administration, the selective delivery, and the term "improved" are therefore unclear and ambiguous, thus rendering the scope of the claimed subject-matter unclear (Article 6 PCT), and furthermore lack sufficient disclosure in the description (Article 5 PCT). Consequently, the desired technical effects as specified in said claims 1-107 cannot be verified by experimentation and thus do not constitute a testable criterion.

In addition, the following functional statement used in claims 1, 5-23, 27-45, 49-66, 70-87, 91-107 does not enable the skilled person to determine which technical features are necessary to perform the stated function: "hydrophobic dopamine agonist". The feature "dopamine agonist" does not provide instructions which are sufficiently clear for an expert to reduce them to practice without undue burden. The result is not one which can be verified directly and positively by tests adequately specified in the description. Moreover, the term "hydrophobic" is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

2.2 The international search report has not been established for part of the claims 1-107.

2.3 Consequently the examination has only been carried out for those part of the claims which appear to be clear, supported and disclosed (Article 34(4)(a)(II) PCT).

Re Item V

1. Reference is made to the following documents:

D1: WO 01 37882 A (ELAN PHARM INC) 31 May 2001 (2001-05-31)
D2: WO 01 13903 A (BOEHRINGER INGELHEIM PHARMA ;BRECHT HANS MICHAEL (DE)) 1 March 2001 (2001-03-01)

2. Novelty and inventive step

Furthermore, as far as the application can be clearly understood, the subject-matter of independent claims 1, 22, 44, 66, 87 is not new in the sense of Article 33(2) PCT. The subject-matter of claims 1, 22, 44, 66 and 87 is understood to concern a method for systemic administration of a hydrophobic dopamine agonist to a mammal, the method comprising delivering the dopamine agonist to the dermis of the mammal.

The document D1 discloses (the references in parentheses applying to this document): intradermal administration of the hydrophobic dopamine agonist fenoldopam (see page 2, lines 25-24, page 7, lines 13-16, and page 8, lines 13-17. The subject-matter of independent claims 1, 22, 44, 66, and 87 is therefore not new Article 33(2) PCT.

The document D2 discloses (the references in parentheses applying to this document): a transdermal plaster with the dopamine agonist (R)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-one (see page 4, paragraph 4, page 4, last paragraph - page 5, paragraph 2, page 5, last paragraph - page 6, paragraph 1, claims 1, 11, 12, 25 and 26). Transdermal administration is understood as being a method for selectively delivering a compound to the dermis. The subject-matter of independent claims 1, 22, 44, 66, and 87 is therefore not new Article 33(2) PCT.

It should be noted that subject-matter that is not novel, cannot be considered to be inventive either. Therefore, the subject-matter of independent claims 1, 22, 44, 66, and 87 does not involve an inventive step in the sense of Article 33(3) PCT.

Dependent claims 2-21, 23-43, 45-65, 67-86, 88-107 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to novelty and/or inventive step (Articles 33(2) and 33(3) PCT). The reasons therefor are that the additional features of the said claims are either directly known from documents D1 and D2, or are a

combination of features obvious to the man skilled in the art in consideration of the disclosure of the prior art named in the present proceedings, or they concern only minor modifications which lie within the normal practice of the man skilled in the art.

3. For the assessment of the present claims 1-107 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Further remarks

The embodiment of the invention described in example 1 and shown in table 4 does not fall within the scope of the claims. The C_{max}, T_{max} and AUC of intradermal administration do not appear to be significantly different from the C_{max}, T_{max} and AUC of a subcutaneous bolus injection. Moreover, on page 30, paragraph 67 it is stated that "Analysis of the data by Heterogeneity of Regression analysis revealed that values obtained following administration to the dermis [...] were [...] different from values obtained following subcutaneous administration". This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

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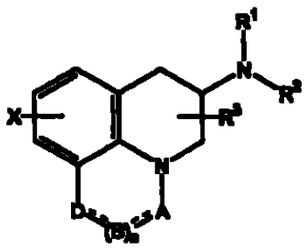
WHAT IS CLAIMED IS:

1. A method for systemic administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising delivering the dopamine agonist by bolus injection to the dermis of the mammal, wherein increased systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

2. The method of claim 1 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

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D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ═ is a single or double bond,

with the proviso that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

3. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

4. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

5. The method of claim 1 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

6. The method of claim 5 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

7. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

8. The method of claim 7 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

9. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

10. The method of claim 1 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

11. The method of claim 10, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

12. The method of claim 10, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

13. The method of claim 10, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

14. The method of claim 10, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

15. The method of claim 1 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

16. The method of claim 15 wherein the delivering is through at least one hollow needle.

17. The method of claim 16 wherein the at least one hollow needle comprises an array of microneedles.

18. The method of claim 17 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

19. The method of claim 1 wherein the hydrophobic dopamine agonist has a $\log P$ of about 2.0 or greater.

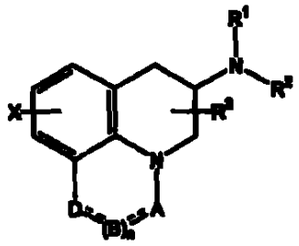
20. The method of claim 1 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

21. A method for administration of a hydrophobic dopamine agonist having a $\log P$ of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal to obtain systemic absorption of the dopamine agonist from the dermis.

22. The method of claim 21 wherein increased systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis by

bolus injection as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

23. The method of claim 22 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ---- is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined

above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, $N-CH_3$;

(2) when n is 0, and

A is CH, $C-SCH_3$, $C-NH_2$, $C-NHCH_3$, $C-NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, $N-CH_3$; then

D is CH_2, C=O, O, NH, $N-CH_3$;

(4) when n is 1, and

A is CH, $C-SCH_3$, $C-NH_2$, $C-NHCH_3$, $C-NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, $N-CH_3$;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

24. The method of claim 23 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*f*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

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25. The method of claim 23 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

26. The method of claim 22 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

27. The method of claim 26 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

28. The method of claim 22 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

29. The method of claim 28 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

30. The method of claim 22 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

31. The method of claim 22 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

32. The method of claim 31, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

33. The method of claim 31, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

34. The method of claim 31, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

35. The method of claim 31, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

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36. The method of claim 22 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

37. The method of claim 22 wherein the delivering is through at least one hollow needle.

38. The method of claim 37 wherein the at least one hollow needle comprises an array of microneedles.

39. The method of claim 37 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

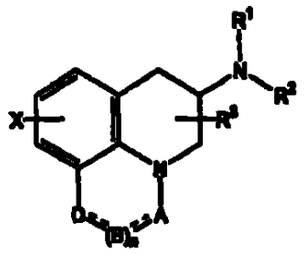
40. The method of claim 22 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

41. The method of claim 22 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

42. A method for administration of a hydrophobic dopamine agonist have a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal wherein systemic absorption of the dopamine agonist from the dermis is obtained.

43. The method of claim 42 wherein increased systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist by bolus injection to the dermis as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

44. The method of claim 43 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{2-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where — is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, $N\text{-}CH_3$; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(4) when n is 1, and

A is CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

45. The method of claim 44 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

46. The method of claim 44 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

47. The method of claim 43 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

48. The method of claim 47 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

49. The method of claim 43 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

50. The method of claim 49 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

51. The method of claim 43 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

52. The method of claim 43 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

53. The method of claim 52, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

54. The method of claim 52, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

55. The method of claim 52, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

56. The method of claim 52, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

57. The method of claim 43 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

58. The method of claim 43 wherein the delivering is through at least one hollow needle.

59. The method of claim 58 wherein the at least one hollow needle comprises an array of microneedles.

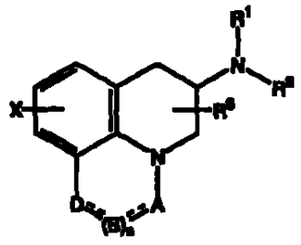
60. The method of claim 58 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

61. The method of claim 43 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

62. The method of claim 43 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

63. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal to achieve a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter $T_{1/2}$ and/or a substantially greater K_e as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

64. The method of claim 63 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl

substituted), C_{2-6} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where — is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH,

$N\text{-}CH_3$; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(4) when n is 1, and

A is CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

65. The method of claim 64 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*f*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

66. The method of claim 64 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*f*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

67. The method of claim 63 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

68. The method of claim 67 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

69. The method of claim 63 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

70. The method of claim 69 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

71. The method of claim 63 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

72. The method of claim 63 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

73. The method of claim 72, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

74. The method of claim 72, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

75. The method of claim 72, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

76. The method of claim 72, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

77. The method of claim 63 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

78. The method of claim 63 wherein the delivering is through at least one hollow needle.

79. The method of claim 78 wherein the at least one hollow needle comprises an array of microneedles.

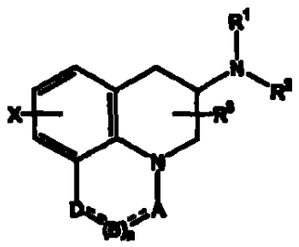
80. The method of claim 78 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

81. The method of claim 63 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

82. The method of claim 63 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

83. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal wherein a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag} and/or a substantially greater K_a is produced as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

84. The method of claim 83 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-6} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or

(C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where — is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

85. The method of claim 84 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

86. The method of claim 84 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

87. The method of claim 83 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

88. The method of claim 87 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

89. The method of claim 83 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

90. The method of claim 89 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

91. The method of claim 83 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

92. The method of claim 83 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

93. The method of claim 92, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

94. The method of claim 92, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

95. The method of claim 92, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

96. The method of claim 92, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

97. The method of claim 83 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

98. The method of claim 83 wherein the delivering is through at least one hollow needle.

99. The method of claim 98 wherein the at least one hollow needle comprises an array of microneedles.

100. The method of claim 98 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

101. The method of claim 83 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

102. The method of claim 83 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

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TRATADO DE COOPERACION DE PATENTES

De la
AUTORIDAD INTERNACIONAL DE EXAMEN PRELIMINAR

PCT

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NOTIFICACION DE LA TRANSMISION DEL REPORTE INTERNACIONAL DE EXAMEN PRELIMINAR
(Regla 71.1 del PCT)

Fecha de presentación *(día/mes/año)* 01.12.2003

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Solicitante
PHARMACIA CORPORATION

1. El solicitante es notificado por la presente, que esta Autoridad Internacional de Examen Preliminar transmite con la misma el reporte internacional de examen preliminar y sus anexos, si hay alguno, establecidos en la solicitud internacional.

2. Una copia del reporte y sus anexos, si hay alguno, está siendo transmitido a la Oficina Internacional para su comunicación a todas las oficinas elegidas.

3. Cuando sea requerido por alguna de las oficinas elegidas, la Oficina Internacional preparará una traducción al inglés del reporte (pero no de alguno de los anexos), y transmitirá dicha traducción a esas oficinas.

4. RECORDATORIO

El solicitante debe entrar a la fase nacional antes de que cada oficina elegida realice ciertos actos (presentación de traducciones y pago de derechos nacionales) dentro de 30 meses a partir de la fecha de prioridad (o después en algunas oficinas) (artículo 39(1)) (véase también el recordatorio enviado por la Oficina Internacional con la forma del PCT/IB/301).

Cuando una traducción de la solicitud internacional deba ser provista a una oficina elegida, la traducción debe contener una traducción de cualquiera de los anexos del reporte internacional de examen preliminar. Es responsabilidad del solicitante, preparar y proveer dicha traducción directamente a cada oficina elegida interesada.

Para más detalles sobre los límites de tiempo aplicables y requisitos de las oficinas elegidas, véase el volumen II de la guía del PCT del solicitante.

Se llama la atención del solicitante respecto al artículo 33(5), que señala que los criterios de paso novedoso y de innovación y la aplicación industrial descritos en el artículo 33(2) a (4), sirven sólo para los propósitos del examen preliminar internacional, y que "cualquier Estado contrayente puede aplicar criterios adicionales y diferentes para los propósitos de decidir si, en ese Estado, las invenciones reclamadas son patentables o no" (véase también el artículo 27(5)). Dichos criterios adicionales pueden relacionarse, por ejemplo, con excenciones de patentabilidad, requisitos para permitir la descripción, claridad y apoyo de las reivindicaciones.

Nombre y dirección de correo de la autoridad internacional de examen preliminar
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TRATADO DE COOPERACION DE PATENTES

PCT

REPORTE INTERNACIONAL DE EXAMEN PRELIMINAR

(artículo 36 y regla 70 del PCT)

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Referencia del archivo del solicitante o agente
6794S-023POB

PARA ACCION ADICIONAL
Véase la notificación de la transmisión del reporte internacional de examen preliminar (forma del PCT/IPEA/416)

Solicitud internacional No.	Fecha de presentación internacional	Datos de prioridad *(día/mes/año)*
PCT/US02/19918	24.06.2002	29.06.2001

Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC
A61M5/158

Solicitante
PHARMACIA CORPORATION

1. Este reporte internacional de examen preliminar ha sido preparado por esta Autoridad Internacional de Examen Preliminar, y es transmitido al solicitante de acuerdo al artículo 36.

2. Este REPORTE consiste de un total de 8 hojas, incluyendo esta hoja.
   ⊛ Este reporte va acompañado también de ANEXOS, es decir, hojas de la descripción, reivindicaciones y/o dibujos que han sido enmendados y son la base de este reporte, y/u hojas que contienen rectificaciones hechas antes que las realizadas por esta autoridad (véase la regla 70.16 y la sección 607 de las instrucciones administrativas bajo el PCT).
   Estos anexos consisten de un total de 19 hojas.

3. Este reporte contiene indicaciones que se refieren a los siguientes ítems:
   I ⊛ Base de la opinión
   II □ Prioridad
   III ⊛ Ninguna formulación de opinión con respecto al paso novedoso y de innovación y la aplicación industrial
   IV □ Falta de unidad de la invención
   V ⊛ Enunciado razonado bajo la regla 66.2(a)(ii) con respecto al paso novedoso y de innovación y la aplicación industrial, citas y explicaciones que sustentan dicho enunciado
   VI □ Ciertos documentos citados
   VII □ Ciertos defectos en la solicitud internacional
   VIII □ Ciertas observaciones en la solicitud internacional

Fecha de presentación de la demanda	Fecha de terminación de este reporte
15.01.2003	01.12.2003

Nombre y dirección de correo de la autoridad internacional de examen preliminar
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REPORTE INTERNACIONAL DE EXAMEN PRELIMINAR

Solicitud Internacional No. PCT/US02/19918

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I. Base del reporte

1. Con respecto a los elementos de la solicitud internacional *(las hojas de reemplazo que se han provisto a la oficina receptora en respuesta a una invitación bajo el artículo 14, son referidas en este reporte como "presentadas originalmente" y no se anexan a este reporte, puesto que no contienen enmiendas (reglas 70.16 y 70.17))*:

   Descripción, páginas
   1 a 32 — como se presentaron originalmente

   Reivindicaciones, números
   1 a 102 — recibidas el día 22.09.2003 con la carta del 19.09.2003

2. Con respecto al idioma, todos los elementos indicados anteriormente eran asequibles o fueron provistos a esta autoridad en el idioma en el que la solicitud internacional se presentó, a menos que se indicara de otra manera bajo este ítem.

   Estos elementos eran asequibles o fueron provistos a esta autoridad en el siguiente idioma, que es:
   ☐ el idioma de una traducción provista para los propósitos de la búsqueda internacional (bajo la regla 23.1(b)).
   ☐ el idioma de publicación de la solicitud internacional (bajo la regla 48.3(b)).
   ☐ el idioma de una traducción provista para los propósitos del examen preliminar internacional (bajo la regla 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia de nucleótidos y/o de aminoácidos descrita en la solicitud internacional, el examen preliminar internacional se llevó a cabo con base en el listado de secuencias:
   ☐ contenido en la solicitud internacional en forma escrita
   ☐ presentado junto con la solicitud internacional en forma legible en computadora
   ☐ provisto después a esta autoridad en forma escrita
   ☐ provisto después a esta autoridad en forma legible en computadora
   ☐ Se ha provisto el enunciado de que el listado de secuencias escrito provisto después, no va más allá de la descripción en la solicitud internacional como se presentó
   ☐ Se ha provisto el enunciado de que la información registrada en forma legible en computadora, es idéntica al listado de secuencias escrito que se ha provisto

4. Las enmiendas han resultado en la cancelación de:

   ☐ la descripción, páginas:
   ☐ las reivindicaciones, Nos.:
   ☐ los dibujos, hojas:

5. ⊛ Este reporte se ha establecido como si (algunas de) las enmiendas no se hubieran hecho, puesto que se ha considerado que van más allá de la descripción presentada (regla 70.2(c)).

   (cualquier hoja de reemplazo que contenga dichas enmiendas, deberá referirse bajo el ítem 1, y deberá anexarse a este reporte)

   Véase hoja aparte

6. Observaciones adicionales, si es necesario.

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REPORTE INTERNACIONAL DE EXAMEN PRELIMINAR Solicitud Internacional No. PCT/US02/19918

III. Ninguna formulación de opinión con respecto al paso novedoso y de innovación y la aplicación industrial

1. Las cuestiones de si la invención reclamada parece ser novedosa para implicar un paso innovador (que será no obvio) o será aplicable industrialmente, no se han examinado con respecto a:
   - ☐ la solicitud internacional completa
   - ⊛ las reivindicaciones 1 a 107 (todas en parte)

   porque:

   ⊛ dicha solicitud internacional, o dichas reivindicaciones 1 a 107 con respecto a la aplicación industrial, se refieren a la siguiente materia que no requiere un examen preliminar internacional (especificar):

   véase hoja aparte

   ⊛ la descripción, las reivindicaciones o los dibujos *(indicar los elementos particulares)* o dichas reivindicaciones 1 a 107 (todas en parte) son tan inciertos, que no pudo formarse una opinión significativa *(especificar)*:

   véase hoja aparte

   - ☐ las reivindicaciones, o dichas reivindicaciones 1 a 107 están sustentadas tan inadecuadamente por la descripción, que no pudo formarse una opinión significativa
   - ☐ no se ha establecido el reporte de búsqueda internacional para dichas reivindicaciones 1 a 107

2. No puede llevarse a cabo un examen preliminar internacional significativo debido a la falla del listado de secuencias de nucleótidos y/o de aminoácidos para cumplir con el estándar provisto en el anexo C de las instrucciones administrativas:
   - ☐ la forma escrita no se ha provisto o no cumple con el estándar
   - ☐ la forma legible en computadora no se ha provisto o no cumple con el estándar

V. Enunciado razonado bajo el artículo 35(2) con respecto al paso novedoso y de innovación o la aplicación industrial, citas y explicaciones que sustentan dicho enunciado

1. Enunciado

Innovación	SI: Reivindicaciones NO: Reivindicaciones 1 a 107
Paso novedoso (IS)	SI: Reivindicaciones NO: Reivindicaciones 1 a 107
Aplicación industrial (IA)	SI: Reivindicaciones NO: Reivindicaciones 1 a 107

2. Citas y explicaciones

Véase hoja aparte

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REPORTE INTERNACIONAL DE EXAMEN PRELIMINAR – HOJA APARTE Solicitud Internacional No. PCT/US02/19918

Item de referencia I

Las enmiendas presentadas con la carta con fecha 19-09-2003, introducen la materia que va más allá del contenido de la solicitud presentada, contrariamente al artículo 34(2)(b) del PCT. Las enmiendas concernientes, son las siguientes: reivindicaciones 1, 22 y 43.

La explicación del solicitante para las enmiendas de las reivindicaciones 1, 22 y 43 no puede aceptarse, ya que el párrafo 50, oración final (página 23, renglones 29 a 31) no puede funcionar como la base para las enmiendas de las reivindicaciones 1, 22 y 43. En el párrafo 50, se describe "absorción incrementada de sustancias inyectadas en la dermis". La materia de las reivindicaciones 1, 22 y 43 difiere de esto, porque no se describe "absorción **sistémica** incrementada". La característica de absorción sistémica incrementada de un agonista de dopamina hidrofóbico que tiene un logP de 1.5 o más después de liberar el agonista de dopamina mediante inyección de bolo a la dermis, no se describe en la solicitud presentada originalmente.

Las siguientes enmiendas, no son contrarias al artículo 34(2)(b) del PCT: reivindicaciones 19, 21, 45, 63 y 83. La base para "liberar el agonista de dopamina mediante inyección de bolo a la dermis", "un agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más" y "un agonista de dopamina hidrofóbico que tiene un logP de alrededor de 2.0 o más", puede encontrarse en las reivindicaciones 1, 7,

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20, 22, 29, 42, 44, 51, 64, 66, 72, 85 y el párrafo 16 de la solicitud presentada originalmente.

Se está llevando a cabo el examen de las reivindicaciones 1 a 107 como se presentaron el 01-04-2003.

Item de referencia III

1. Las reivindicaciones 1 a 107 se refieren a la materia considerada por esta autoridad que es cubierta por las provisiones de la regla 67.1(iv) del PCT. En consecuencia, no se formulará opinión alguna con respecto a la aplicación industrial de la materia de esas reivindicaciones (artículo 34(4)(a)(i) del PCT).

2. Las reivindicaciones 1 a 107 (todas en parte) no cumplen con los requisitos del artículo 6 del PCT, porque no se define la materia para la cual se busca la protección.

2.1 Las reivindicaciones 1 a 107 intentan definir la materia en términos del resultado que se logrará, a saber, "se produce absorción sistémica mejorada en comparación con la absorción lograda después de liberar el agonista de dopamina subcutáneamente mediante inyección de bolo", o "liberando selectivamente el agonista de dopamina a la dermis", o "una biodisponibilidad sustancialmente mayor y/o una $C_{máx}$ sustancialmente mayor y/o un $T_{máx}$ sustancialmente más corto y/o un pKa sustancialmente mayor, en comparación con los que se obtienen después de la administración subcutánea de bolo del agonista de dopamina a una dosis idéntica". Estas características no dan instrucciones que sean

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suficientemente claras para que un experto las reduzca a la práctica sin carga indebida.

La descripción no especifica los métodos experimentales y las condiciones bajo las cuales debe llevarse a cabo la comparación con la administración subcutánea de bolo. Además, no se especifican pruebas por las cuales los resultados de la comparación con la administración subcutánea de bolo, o la liberación selectiva hacia la dermis, pueden verificarse directa y positivamente. No se especifica el método de administración intradérmica, el método de administración subcutánea, la especie, los sujetos, el número de sujetos, el diseño experimental de los estudios, los métodos de prueba, las condiciones de los estudios y el método de cálculo de los parámetros. Para los parámetros $T_{máx}$, $C_{máx}$ y T_{lag}, no se especifica si se determinan en sangre, plasma, orina u otro fluido corporal. Para el parámetro de biodisponibilidad, no se especifica si significa biodisponibilidad relativa o absoluta. Además, la definición de la biodisponibilidad dada en la página 7, párrafo 18 de la descripción, no está de acuerdo con la definición usada en general, debido a que el cálculo no se basa en la dosificación y el AUC (o depuración) de una dosis intravenosa y una dosis extravascular, ni se establece la condición de que la depuración deba continuar siendo constante.

Además, es claro a partir de la descripción de los párrafos 20, 40 a 41 y 43, que las siguientes características son esenciales para la definición de la invención:

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(1) la administración en la dermis y la administración en el sitio de referencia tal como el tejido subcutáneo, implican la misma cantidad y concentración de fármaco, así como el mismo vehículo;

(2) la comparación entre la administración en la dermis y la administración en el sitio de referencia tal como el tejido subcutáneo, debe ser al mismo régimen de administración en términos de cantidad y volumen por unidad de tiempo;

(3) la profundidad de colocación de la sustancia en la dermis debe ser a una profundidad de por lo menos 0.3 mm, hasta una profundidad no mayor de aproximadamente 2.5 mm;

(4) la $T_{máx}$ es un valor que representa el tiempo para lograr la concentración máxima del compuesto en sangre; y

(5) la Cmáx es un valor que representa la concentración máxima del compuesto en sangre.

Puesto que las reivindicaciones independientes 1, 22, 44, 66 y 87 no contienen estas características, no cumplen con el siguiente requisito del artículo 6 del PCT tomado en combinación con la regla 6.3(b) del PCT, de que toda reivindicación independiente debe contener todas las características técnicas esenciales para la definición de la invención.

Además, el término "mejorada" que se usa en las reivindicaciones 1, 11, 23, 33, 45, 55, 76 y 97, es vago e incierto. No está claro si el término "mejorada" significa un incremento o una disminución, o

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ambos. Este término deja al lector con dudas acerca del significado de la característica técnica a la cual se refiere, haciendo de esta manera que la definición de la materia de dichas reivindicaciones, sea incierta (artículo 6 del PCT).

Las definiciones de los parámetros, la referencia a la administración subcutánea de bolo, la liberación selectiva y el término "mejorada" son por lo tanto inciertos y ambiguos, haciendo de esta manera que el alcance de la materia reclamada, sea incierto (artículo 6 del PCT), y carecen además de descripción suficiente en la descripción (artículo 5 del PCT). Por consiguiente, los efectos técnicos deseados especificados en dichas reivindicaciones 1 a 107 no pueden verificarse mediante experimentación, y de esta manera no constituyen un criterio verificable.

Además, el siguiente enunciado funcional usado en las reivindicaciones 1, 5 a 23, 27 a 45, 49 a 66, 70 a 87 y 91 a 107 no permite que el experto en la técnica determine qué características técnicas son necesarias para realizar la función enunciada: "agonista de dopamina hidrofóbico". La característica "agonista de dopamina" no da instrucciones que sean suficientemente claras para que el experto las reduzca a la práctica sin carga indebida. El resultado no es uno que pueda verificarse directa y positivamente mediante pruebas especificadas adecuadamente en la descripción. Además, el término "hidrofóbico" es vago e incierto, y deja al lector con dudas acerca del significado de la característica técnica a la cual se refiere, haciendo de esta manera que la definición de la materia de dichas reivindicaciones, sea incierta (artículo 6 del PCT).

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2.2 No se ha establecido el reporte de búsqueda internacional como parte de las reivindicaciones 1 a 107.

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2.3 En consecuencia, el examen sólo se ha llevado a cabo para aquellas partes de las reivindicaciones que parecen ser claras, sustentadas y descritas (artículo 34(4)(a)(ii) del PCT).

Item de referencia V

1. Se hace referencia a los siguientes documentos:

D1: WO 01 37882 A (ELAN PHARM INC), 31 de mayo de 2001.

D2: WO 01 13903 A (BOEHRINGER INGELHEIM PHARMA; BRECHT HANS MICHAEL (DE)), 1 de marzo de 2001.

2. Paso novedoso y de innovación

Además, en cuanto a la solicitud, puede entenderse claramente que la materia de las reivindicaciones independientes 1, 22, 44, 66 y 87, no es nueva en el sentido del artículo 33(2) del PCT. Se entiende que la materia de las reivindicaciones 1, 22, 44, 66 y 87 se refiere a un método para la administración sistémica de un agonista de dopamina hidrofóbico a un mamífero, el método comprendiendo liberar el agonista de dopamina a la dermis del mamífero.

El documento D1 describe (las referencias entre paréntesis se aplican a este documento): administración intradérmica del agonista de dopamina hidrofóbico fenoldopam (véase la página 2, renglones 25 a 24; página 7, renglones 13 a 16; y página 8, renglones 13 a 17. La materia de

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las reivindicaciones independientes 1, 22, 44, 66 y 87, no es por lo tanto nueva en el sentido del artículo 33(2) del PCT.

El documento D2 describe (las referencias entre paréntesis se aplican a este documento): un emplasto transdérmico con el agonista de dopamina (R)-5,6-dihidro-5-(metilamino)-4H-Imidazo[4,5-*ij*]-quinolin-2(1H)-ona (véase la página 4, párrafo 4; página 4, último párrafo; página 5, párrafo 2; página 5, último párrafo; página 6, párrafo 1; reivindicaciones 1, 11, 12, 25 y 26). Se entiende que la administración transdérmica es un método para liberar selectivamente un compuesto hacia la dermis. La materia de las reivindicaciones independientes 1, 22, 44, 66 y 87, no es por lo tanto nueva en el sentido del artículo 33(2) del PCT.

Debe observarse que la materia que no sea novedosa, no puede considerarse como innovadora. Por lo tanto, la materia de las reivindicaciones independientes 1, 22, 44, 66 y 87, no implica un paso novedoso en el sentido del artículo 33(3) del PCT.

Las reivindicaciones dependientes 2 a 21, 23 a 43, 45 a 65, 67 a 86 y 88 a 107 no parecen contener característica adicional alguna que, en combinación con las características de cualquier reivindicación a la cual se refieren, cumplen con los requisitos del PCT con respecto a paso novedoso y de innovación (artículos 33(2) y 33(3) del PCT). Las razones son por lo tanto que las características adicionales de dichas reivindicaciones se conocen directamente de los documentos D1 y D2, o son una combinación de características obvias para los expertos en la técnica al considerar la descripción de la técnica anterior nombrada en los

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presentes acontecimientos, o se refieren sólo a modificaciones menores que están dentro de la práctica normal de los expertos en la técnica.

3. Para evaluar las presentes reivindicaciones 1 a 107 sobre la cuestión de si son industrialmente aplicables, no existen criterios unificados en los estados contrayentes del PCT. La patentabilidad puede depender también de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable la materia de las reivindicaciones para el uso de un compuesto en el tratamiento médico, pero puede permitir sin embargo reivindicaciones para un compuesto conocido para primer uso en el tratamiento médico, y el uso de dicho compuesto en la fabricación de un medicamento para un tratamiento médico nuevo.

4. Otras observaciones

La modalidad de la invención descrita en el ejemplo 1 y mostrada en el cuadro 4, no está dentro del alcance de las reivindicaciones. La $C_{máx}$, el $T_{máx}$ y el AUC de la administración intradérmica, no parecen ser significativamente diferentes de la $C_{máx}$, el $T_{máx}$ y el AUC de una inyección subcutánea de bolo. Además, en la página 30, párrafo 67, se establece que "el análisis de los datos mediante el análisis de heterogeneidad de regresión, reveló que los valores obtenidos después de la administración a la dermis [...] fueron [...] diferentes de los valores obtenidos después de la administración subcutánea". Esta inconsistencia entre las reivindicaciones y la descripción, deja dudas

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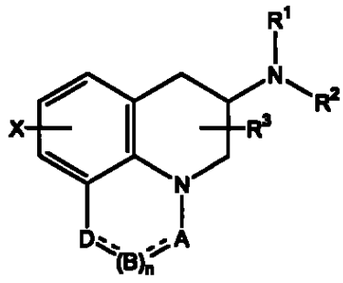
acerca de la materia para la cual se busca la protección, haciendo de esta manera que las reivindicaciones sean inciertas (artículo 6 del PCT).

1.- Un método para la administración sistémica de un agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más a un mamífero, el método caracterizado porque comprende liberar el agonista de dopamina mediante inyección de bolo a la dermis del mamífero, en donde se logra absorción sistémica incrementada en comparación con la absorción producida tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

2.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF,

CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ——— es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo, al humano.

3.- El método de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

4.- El método de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-

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(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona,, o una sal farmacéuticamente aceptable del mismo.

5.- El método de conformidad con la reivindicación 1, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

6.- El método de conformidad con la reivindicación 5, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

7.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

8.- El método de conformidad con la reivindicación 7, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 2 minutos.

9.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

10.- El método de conformidad con la reivindicación 1, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

11.- El método de conformidad con la reivindicación 10,

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caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

12.- El método de conformidad con la reivindicación 10, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

13.- El método de conformidad con la reivindicación 10, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

14.- El método de conformidad con la reivindicación 10, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

15.- El método de conformidad con la reivindicación 1, caracterizado además porque la liberación es a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

16.- El método de conformidad con la reivindicación 15, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

17.- El método de conformidad con la reivindicación 16, caracterizado además porque la aguja hueca (por lo menos una) comprende una disposición de microagujas.

18.- El método de conformidad con la reivindicación 17, caracterizado además porque el agonista de dopamina se libera mediante

bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

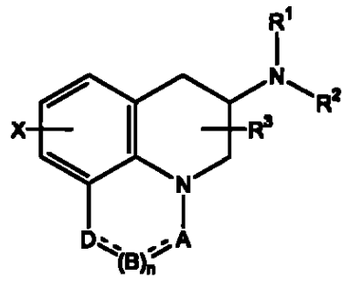
19.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 2.0 o más.

20.- El método de conformidad con la reivindicación 1, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

21.- Un método para la administración de un agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más a un mamífero, el método caracterizado porque comprende liberar selectivamente el agonista de dopamina mediante inyección de bolo a la dermis del mamífero, para lograr absorción sistémica del agonista de dopamina a partir de la dermis.

22.- El método de conformidad con la reivindicación 21, caracterizado además porque la absorción sistémica incrementada del agonista de dopamina se produce tras liberar el agonista de dopamina a la dermis mediante inyección de bolo en comparación con la absorción producida tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

23.- El método de conformidad con la reivindicación 22, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde —— es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-

(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo, al humano.

24.- El método de conformidad con la reivindicación 23, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

25.- El método de conformidad con la reivindicación 23, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona,, o una sal farmacéuticamente aceptable del mismo.

26.- El método de conformidad con la reivindicación 22, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

27.- El método de conformidad con la reivindicación 26, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

28.- El método de conformidad con la reivindicación 22, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

29.- El método de conformidad con la reivindicación 28, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 2 minutos.

30.- El método de conformidad con la reivindicación 22, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

31.- El método de conformidad con la reivindicación 22, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

32.- El método de conformidad con la reivindicación 31, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

33.- El método de conformidad con la reivindicación 31, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

34.- El método de conformidad con la reivindicación 31, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

35.- El método de conformidad con la reivindicación 31, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

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36.- El método de conformidad con la reivindicación 22, caracterizado además porque la liberación es a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

37.- El método de conformidad con la reivindicación 22, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

38.- El método de conformidad con la reivindicación 37, caracterizado además porque la aguja hueca (por lo menos una) comprende una disposición de microagujas.

39.- El método de conformidad con la reivindicación 37, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

40.- El método de conformidad con la reivindicación 22, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 2.0 o más.

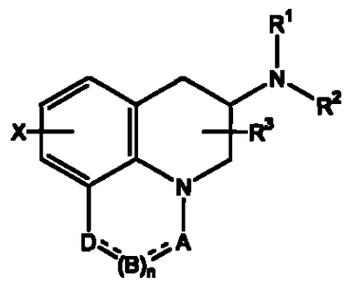
41.- El método de conformidad con la reivindicación 22, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

42.- Un método para la administración de un agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más a un mamífero, el método caracterizado porque comprende liberar selectivamente

el agonista de dopamina mediante inyección de bolo a la dermis del mamífero, en donde se logra absorción sistémica del agonista de dopamina a partir de la dermis.

43.- El método de conformidad con la reivindicación 42, caracterizado además porque la absorción sistémica incrementada del agonista de dopamina se produce tras liberar el agonista de dopamina a la dermis mediante inyección de bolo en comparación con la absorción producida tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

44.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6},

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CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ——— es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo, al humano.

45.- El método de conformidad con la reivindicación 44, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

46.- El método de conformidad con la reivindicación 44,

caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona,, o una sal farmacéuticamente aceptable del mismo.

47.- El método de conformidad con la reivindicación 43, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

48.- El método de conformidad con la reivindicación 47, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

49.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

50.- El método de conformidad con la reivindicación 49, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 2 minutos.

51.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

52.- El método de conformidad con la reivindicación 43, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

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53.- El método de conformidad con la reivindicación 52, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

54.- El método de conformidad con la reivindicación 52, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

55.- El método de conformidad con la reivindicación 52, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

56.- El método de conformidad con la reivindicación 52, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

57.- El método de conformidad con la reivindicación 43, caracterizado además porque la liberación es a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

58.- El método de conformidad con la reivindicación 43, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

59.- El método de conformidad con la reivindicación 58, caracterizado además porque la aguja hueca (por lo menos una) comprende una disposición de microagujas.

60.- El método de conformidad con la reivindicación 58,

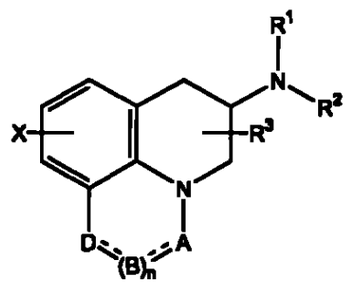
caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

61.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 2.0 o más.

62.- El método de conformidad con la reivindicación 43, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

63.- Un método para la administración de un agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más a un mamífero, el método caracterizado porque comprende liberar selectivamente el agonista de dopamina mediante inyección de bolo a la dermis del mamífero, para lograr una biodisponibilidad sustancialmente mayor y/o una $C_{máx}$ sustancialmente mayor y/o un $T_{máx}$ sustancialmente más corto y/o un T_{lag} sustancialmente más corto y/o un pKa sustancialmente mayor, en comparación con los que se obtienen tras la administración subcutánea de bolo del agonista de dopamina a una dosis idéntica.

64.- El método de conformidad con la reivindicación 63, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ——— es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es

CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo, al humano.

65.- El método de conformidad con la reivindicación 64, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

66.- El método de conformidad con la reivindicación 64, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona,, o una sal farmacéuticamente aceptable del mismo.

67.- El método de conformidad con la reivindicación 63, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 10 minutos.

68.- El método de conformidad con la reivindicación 67, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

69.- El método de conformidad con la reivindicación 63, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

70.- El método de conformidad con la reivindicación 69, caracterizado además porque el agonista de dopamina hidrofóbico se libera a

la dermis en no más de 2 minutos.

71.- El método de conformidad con la reivindicación 63, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

72.- El método de conformidad con la reivindicación 63, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

73.- El método de conformidad con la reivindicación 72, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

74.- El método de conformidad con la reivindicación 72, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en $T_{máx}$.

75.- El método de conformidad con la reivindicación 72, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

76.- El método de conformidad con la reivindicación 72, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

77.- El método de conformidad con la reivindicación 63, caracterizado además porque la liberación es a través de un microporo

cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

78.- El método de conformidad con la reivindicación 63, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

79.- El método de conformidad con la reivindicación 78, caracterizado además porque la aguja hueca (por lo menos una) comprende una disposición de microagujas.

80.- El método de conformidad con la reivindicación 78, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

81.- El método de conformidad con la reivindicación 63, caracterizado además porque el agonista de dopamina hidrofóbico tiene un logP de aproximadamente 2.0 o más.

82.- El método de conformidad con la reivindicación 63, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

83.- Un método para la administración de un agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más a un mamífero, el método caracterizado porque comprende liberar selectivamente el agonista de dopamina mediante inyección de bolo a la dermis del mamífero, en donde se logra una biodisponibilidad sustancialmente mayor y/o una $C_{máx}$

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sustancialmente mayor y/o un $T_{máx}$ sustancialmente más corto y/o un T_{lag} sustancialmente más corto y/o un pKa sustancialmente mayor, en comparación con los que se obtienen después de la administración subcutánea de bolo del agonista de dopamina a una dosis idéntica.

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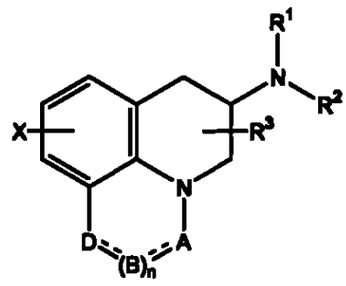
84.- El método de conformidad con la reivindicación 83, caracterizado además porque el agonista de dopamina es como se describe en la fórmula (I):



(I)

o sales farmacéuticamente aceptables del mismo, en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ═══ es un enlace sencillo o doble enlace, con

las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo, al humano.

85.- El método de conformidad con la reivindicación 84, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, o una sal farmacéuticamente aceptable del mismo.

86.- El método de conformidad con la reivindicación 84, caracterizado además porque el agonista de dopamina es (*R*)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona,, o una sal farmacéuticamente aceptable del mismo.

87.- El método de conformidad con la reivindicación 83, caracterizado además porque la inyección subcutánea de bolo se libera en no

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más de 10 minutos.

88.- El método de conformidad con la reivindicación 87, caracterizado además porque la inyección subcutánea de bolo se libera en no más de 2 minutos.

89.- El método de conformidad con la reivindicación 83, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 10 minutos.

90.- El método de conformidad con la reivindicación 89, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis en no más de 2 minutos.

91.- El método de conformidad con la reivindicación 83, caracterizado además porque el agonista de dopamina hidrofóbico se libera a la dermis mediante inyección de bolo repetida.

92.- El método de conformidad con la reivindicación 83, caracterizado además porque por lo menos un parámetro farmacocinético se mejora tras liberar el agonista de dopamina a la dermis en comparación con el mismo parámetro farmacocinético tras liberar el agonista de dopamina subcutáneamente mediante inyección de bolo.

93.- El método de conformidad con la reivindicación 92, caracterizado además porque el parámetro farmacocinético mejorado comprende biodisponibilidad incrementada del agonista de dopamina.

94.- El método de conformidad con la reivindicación 92, caracterizado además porque el parámetro farmacocinético mejorado

comprende una disminución en $T_{máx}$.

95.- El método de conformidad con la reivindicación 92, caracterizado además porque el parámetro farmacocinético mejorado comprende un incremento en $C_{máx}$.

96.- El método de conformidad con la reivindicación 92, caracterizado además porque el parámetro farmacocinético mejorado comprende una disminución en T_{lag}.

97.- El método de conformidad con la reivindicación 83, caracterizado además porque la liberación es a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

98.- El método de conformidad con la reivindicación 83, caracterizado además porque la liberación es a través de por lo menos una aguja hueca.

99.- El método de conformidad con la reivindicación 98, caracterizado además porque la aguja hueca (por lo menos una) comprende una disposición de microagujas.

100.- El método de conformidad con la reivindicación 98, caracterizado además porque el agonista de dopamina se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

101.- El método de conformidad con la reivindicación 83, caracterizado además porque el agonista de dopamina hidrofóbico tiene un

logP de aproximadamente 2.0 o más.

102.- El método de conformidad con la reivindicación 83, caracterizado además porque el agonista de dopamina está en forma de nanopartículas o nanocristales.

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

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Applicant's or agent's file reference *(if desired) (12 characters maximum)* 6794S-023POB

Box No. I TITLE OF INVENTION

ENHANCED PARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PHARMACIA CORPORATION
Corporate Patent Department
800 North Lindbergh Blvd., Mail Zone One
St. Louis, Missouri 63167
United States of America

Telephone No. 847-581-5144

Facsimile No. 847-581-6881

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PINKERTON, Thomas C.
2400 Ridgeview Drive
Kalamazoo, MI 49008
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HOLLAND, DONALD R.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, MO 63105
United States of America

Telephone No. 314-726-7500

Facsimile No. 314-726-7501

Teleprinter No.

Agent's registration No. with the Office 35,197

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GM Gambia	☒ NZ New Zealand
☒ AG Antigua and Barbuda	☒ HR Croatia	☒ OM Oman
☒ AL Albania	☒ HU Hungary	☒ PH Philippines
☒ AM Armenia	☒ ID Indonesia	☒ PL Poland
☒ AT Austria	☒ IL Israel	☒ PT Portugal
☒ AU Australia	☒ IN India	☒ RO Romania
☒ AZ Azerbaijan	☒ IS Iceland	☒ RU Russian Federation
☒ BA Bosnia and Herzegovina	☒ JP Japan	
☒ BB Barbados	☒ KE Kenya	☒ SD Sudan
☒ BG Bulgaria	☒ KG Kyrgyzstan	☒ SE Sweden
☒ BR Brazil	☒ KP Democratic People's Republic of Korea	☒ SG Singapore
☒ BY Belarus		☒ SI Slovenia
☒ BZ Belize	☒ KR Republic of Korea	☒ SK Slovakia
☒ CA Canada	☒ KZ Kazakhstan	☒ SL Sierra Leone
☒ CH & LI Switzerland and Liechtenstein	☒ LC Saint Lucia	☒ TJ Tajikistan
☒ CN China	☒ LK Sri Lanka	☒ TM Turkmenistan
☒ CO Colombia	☒ LR Liberia	☒ TN Tunisia
☒ CR Costa Rica	☒ LS Lesotho	☒ TR Turkey
☒ CU Cuba	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☒ LU Luxembourg	
☒ DE Germany	☒ LV Latvia	☒ TZ United Republic of Tanzania
☒ DK Denmark	☒ MA Morocco	☒ UA Ukraine
☒ DM Dominica	☒ MD Republic of Moldova	☒ UG Uganda
☒ DZ Algeria		☒ US United States of America
☒ EC Ecuador	☒ MG Madagascar	
☒ EE Estonia	☒ MK The former Yugoslav Republic of Macedonia	☒ UZ Uzbekistan
☒ ES Spain		☒ VN Viet Nam
☒ FI Finland	☒ MN Mongolia	☒ YU Yugoslavia
☒ GB United Kingdom	☒ MW Malawi	☒ ZA South Africa
☒ GD Grenada	☒ MX Mexico	☒ ZM Zambia
☒ GE Georgia	☒ MZ Mozambique	☒ ZW Zimbabwe
☒ GH Ghana	☒ NO Norway	

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☐	☒ All other countries included in the PCT	☐
☐	☐	☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Continuation of Box No. IV

TELSCHER, Rudolph A.
WHEELOCK, Bryan K.
WALSH, Joseph E.
GRYTE, David M.
SOTIRIOU, Evan R.
ODELL, Elizabeth D.
BURRIS, Kelly K.
CASSEL, Alan
CUTLER, Matthew
GRAY, Scott
FUSSNER, Anthony G.
ZACKSON, Saul L.
WILLIAMS, Scott A.
KEANE, Timothy J.
FORBES, James C.
WARNER, James R. Michael

Continuation of Box No. V

US - Continuation-in-part of 09/897,801 filed 29 June 2001

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Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 29 June 2001	09/897,801	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* *Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EP .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*:		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	5
description (excluding sequence listing part)	:	32
claims	:	19
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	57
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	57

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(i), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:	Number of items
1. ☒ fee calculation sheet	:
2. ☐ original separate power of attorney	:
3. ☐ original general power of attorney	:
4. ☐ copy of general power of attorney; reference number, if any:	:
5. ☐ statement explaining lack of signature	:
6. ☐ priority document(s) identified in Box No. VI as item(s):	:
7. ☐ translation of international application into *(language)*:	:
8. ☐ separate indications concerning deposited microorganism or other biological material	:
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))	
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:
10. ☒ other *(specify)*: Transmittal Letter to USPTO	:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

HOLLAND, DONALD R. (Agent)
Reg. No. 35,197

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

201

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 6794S-023POB

Applicant: Pharmacia Corporation - Skokie

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE	240 T	
2. SEARCH FEE	866 S	

International search to be carried out by EP

(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)

3. INTERNATIONAL FEE

Basic Fee

Where item (b) of Box No. IX applies, enter Sub-total number of sheets / Where item (b) of Box No. IX does not apply, enter Total number of sheets: 57

b1 first 30 sheets	407 b1	
b2 27 (number of sheets in excess of 30) x 9 (fee per sheet) =	243 b2	
b3 additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)): 400 x ____ (fee per sheet) =	b3	
Add amounts entered at b1, b2and b3 and enter total at B	640 B	

Designation Fees

The international application contains ALL designations.

5 (number of designation fees payable *(maximum 5)*) x 88 (amount of designation fee) =	440 D	
Add amounts entered at B and Dand enter total at I	1080 I	

(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 75% of the sum of the amounts entered at B and D.)

4. FEE FOR PRIORITY DOCUMENT *(if applicable)*	15 P	
5. TOTAL FEES PAYABLE / Add amounts entered at T, S, I and P, and enter total in the TOTAL box	2201 TOTAL	

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons

☒ cheque ☐ bank draft ☐ revenue stamps ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all receiving Offices)

Receiving Office: RO/ US

Deposit Account No.: 08-0750

Date: 24 June 2002

Name: Donald R. Holland

Signature: Donald R Holland

☐ Authorization to charge the total fees indicated above.

☒ *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

☐ Authorization to charge the fee for priority document.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION

Applicant's or agent's file reference: 6794S-023POB

International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US02/19918	24/06/2002	29/06/2001

Title of invention: ENHANCED PARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PHARMACIA CORPORATION
Corporate Patent Department
800 North Lindbergh Blvd., Mail Zone One
St. Louis, Missouri 63167
United States of America

Telephone No.: 847-581-5144
Facsimile No.: 847-581-6881
Teleprinter No.:
Applicant's registration No. with the Office:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PINKERTON, Thomas C.
2400 Ridgeview Drive
Kalamazoo, MI 49008
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US02/19918

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HOLLAND, DONALD R.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, MO 63105
United States of America

Telephone No.
314-726-7500

Facsimile No.
314-726-7501

Teleprinter No.

Agent's registration No. with the Office
35,197

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[X] the international application as originally filed

the description
- [X] as originally filed
- [ ] as amended under Article 34

the claims
- [X] as originally filed
- [ ] as amended under Article 19 (together with any accompanying statement)
- [ ] as amended under Article 34

the drawings
- [X] as originally filed
- [ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- [X] which is the language in which the international application was filed.
- [ ] which is the language of a translation furnished for the purposes of international search.
- [ ] which is the language of publication of the international application.
- [ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby **elects all eligible States** *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

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Sheet No. .3

International application No.
PCT/US02/19918

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listings in computer readable form
7. ☐ tables in computer readable form related to sequence listings
8. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Donald R. Holland

HOLLAND, DONALD R. (Agent)
Reg. No. 35,197

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

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CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/19918	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 6794S-023POB	Date stamp of the IPEA

Applicant

PHARMACIA CORPORATION

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	1530	P	
2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)*	159	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	1689 TOTAL		

MODE OF PAYMENT

☒ authorization to charge deposit account with the IPEA (see below)	☐ cash
☐ cheque	☐ revenue stamps
☐ postal money order	☐ coupons
☐ bank draft	☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

(This mode of payment may not be available at all IPEAs)

IPEA/ EP

☒ Authorization to charge the total fees indicated above.

☐ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 28300413

Date: January 15, 2003

Name: Donald R. Holland

Signature: Donald R Holland

67945-000023/POB

Search report due 7-7-03

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION (PCT Rule 44.1)

To:
HARNESS, DICKEY & PIERCE P.L.C.
Attn. Holland, Donald R.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
UNITED STATES OF AMERICA

RECEIVED
JAN 21 2003
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

	Date of mailing (day/month/year) 13/01/2003
Applicant's or agent's file reference 67945-023POB	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 02/ 19918	International filing date (day/month/year) 24/06/2002
Applicant PHARMACIA CORPORATION	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

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

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

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

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

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

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

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	John De Bruijn

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

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

Where not to file the amendments?

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

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

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

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

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

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

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

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

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

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

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

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

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

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

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

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

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

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
6794S-023POB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 02/19918	24/06/2002	29/06/2001
Applicant		
PHARMACIA CORPORATION		

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

This International Search Report consists of a total of 6 sheets.

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

1. **Basis of the report**

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

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

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

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

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

2. [X] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS

5. With regard to the abstract,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

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

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/19918

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/158 A61M37/00 A61K9/70

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61M A61N

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 37882 A (ELAN PHARM INC) 31 May 2001 (2001-05-31) page 2, line 24 - line 25 page 7, line 13 - line 16 page 8, line 13 - line 17 -/--	1,5-15, 20,22, 23, 27-37, 42,44, 45, 49-59, 64,66, 70-80, 85,87, 91-101, 106

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 December 2002	13/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Marttin, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/19918

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 13903 A (BOEHRINGER INGELHEIM PHARMA ;BRECHT HANS MICHAEL (DE)) 1 March 2001 (2001-03-01) page 4, paragraph 4 page 4, last paragraph -page 5, paragraph 2 page 4, last paragraph -page 6, paragraph 1; claims 1,11,12,25,26	1-16,20, 22-38, 42, 44-60, 64, 66-81, 85, 87-102, 106
A	US 5 997 501 A (KELLY JOHN GERARD ET AL) 7 December 1999 (1999-12-07) the whole document	1-107
A	WO 00 74763 A (GEORGIA TECH RES CORP) 14 December 2000 (2000-12-14) the whole document	1-106
A	BRESSOLLE F ET AL: "A Weibull distribution model for intradermal administration of ceftazidime." JOURNAL OF PHARMACEUTICAL SCIENCES. UNITED STATES NOV 1993, vol. 82, no. 11, November 1993 (1993-11), pages 1175-1178, XP002225051 ISSN: 0022-3549 cited in the application the whole document	1-106
P,X	WO 01 52854 A (BOEHRINGER INGELHEIM PHARMA ;BRECHT HANS MICHAEL (DE); JUNG BIRGIT) 26 July 2001 (2001-07-26) page 3, line 26 - line 36 page 4, line 23 - line 27 page 5, line 27 - line 33 page 6, line 4 - line 14	1,5-18, 20, 22-24, 27-40, 42,44, 49-62, 64,66, 70-83, 85,87, 91-104, 106

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1, 5-23, 27-45, 49-66, 70-87, 91-107 relate to a compound, defined by reference to a desirable characteristic or property, namely a "hydrophobic dopamine agonist". The term "hydrophobic dopamine agonist" defines the active agent by its pharmacological effect. However, a compound canot be sufficiently characterised by its pharmacological effect as it is done by an expression like "hydrophobic dopamine agonist", because it is impossible to know which substances are encompassed in this expression.

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds prepared in example 1, those mentioned in claims 2-4, 24-26, 46-48, 67-69 and 88-90, those mentioned in the description at page 12, line 12 - page 13, line 8, and the concept of a hydrophobic dopamine agonist.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/19918

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-107 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/19918

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0137882	A	31-05-2001	AU	3440601 A	04-06-2001
			WO	0137882 A2	31-05-2001
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			AU	6836500 A	19-03-2001
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			AU	1076395 A	06-06-1995
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			WO	0152854 A1	26-07-2001
			US	2001034320 A1	25-10-2001

67945-00002 08
2 month response due 4/3/03

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
Holland, Donald R.
HARNESS, DICKEY & PIERCE P.L.C.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
ETATS-UNIS D'AMERIQUE

RECEIVED
FEB 12 2003
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

WRITTEN OPINION
(PCT Rule 66)

Date of mailing (day/month/year)	03/02/2003
Applicant's or agent's file reference: 6794S-023POB	REPLY DUE: within 2 / 00 months/days from the above date of mailing

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 02/ 19918	24/06/2002	29/06/2001

International Patent Classification (IPC) or both national classification and IPC
A61M5/158

Applicant
PHARMACIA CORPORATION

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29/10/2003

Name and mailing address of the IPEA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Netherlands Tel.: (+31-70) 340-2040 Fax: (+31-70) 340-3016	Examiner Formalities officer (incl. extension of time limits) Tel. (+49-89) 2399 2828

Form PCT/IPEA/408 (cover sheet) (march 2002)

I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

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IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International Application No.:	PCT/US02/19918
International Filing Date:	24 June 2002
Applicant:	Pharmacia Corporation
Title:	ENHANCED PARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS (title as established by the Authority)
Attorney Docket:	6794S-000023POB

European Patent Office
IPEA
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
NETHERLANDS

AMENDMENT UNDER ARTICLE 34 AND RESPONSE TO WRITTEN OPINION

This paper is submitted in response the IPEA's written opinion dated February 3, 2003 and it is accompanied by replacement sheets 35, 36, 39-44, and 46-51 submitted herewith.

Claim Amendments Under Art. 34(2)b) PCT:

Claims 13-15, 18, 35-37, 39-41, 45-65, 67-86, and 88-107 are replaced by amended claims bearing the same numbers. Claims 1-12, 16, 17, 19-34, 38, 42-44, 66, and 87 are unchanged. No new claims have been added.

The amended claims were amended solely to correct typographical errors in claim dependencies. No other changes have been made to the claims. Thus,

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support for the subject matter of the amended claims will be found in the correspondingly numbered claims of the original application as well as elsewhere in the specification.

The changes made to the amended claims are indicated below. Deletions are shown within [brackets] and additions are underlined.

13. The method of claim [10] 11, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

14. The method of claim [10] 11, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

15. The method of claim [10] 11, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

18. The method of claim [1] 17 wherein the at least one hollow needle comprises an array of microneedles.

35. The method of claim [32] 33, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

36. The method of claim [32] 33, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

37. The method of claim [32] 33, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

39. The method of claim [38] 23 wherein the delivering is through at least one hollow needle.

40. The method of claim [23] 39 wherein the at least one hollow needle comprises an array of microneedles.

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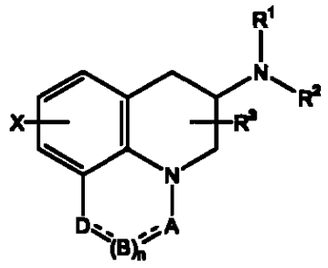
41. The method of claim [40] 39 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

45. The method of claim [42] 44 wherein improved systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

46. The method of claim [43] 45 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined

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above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

47. The method of claim [44] 46 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

48. The method of claim [44] 46 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

49. The method of claim [43] 45 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

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50. The method of claim [47] 49 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

51. The method of claim [43] 45 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

52. The method of claim [49] 51 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

53. The method of claim [50] 52 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

54. The method of claim [43] 45 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

55. The method of claim [43] 45 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

56. The method of claim [53] 55, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

57. The method of claim [52] 55, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

58. The method of claim [52] 55, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

59. The method of claim [52] 55, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

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60. The method of claim [43] 45 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

61. The method of claim [58] 45 wherein the delivering is through at least one hollow needle.

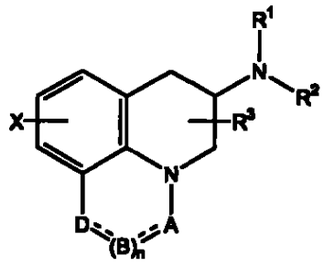
62. The method of claim [43] 61 wherein the at least one hollow needle comprises an array of microneedles.

63. The method of claim [60] 61 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Bellevi611le spring, iontophoresis, or sonophoresis.

64. The method of claim [43] 45 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

65. The method of claim [43] 45 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

67. The method of claim [64] 66 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl

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or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

68. The method of claim [65] 67 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

69. The method of claim [65] 67 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

70. The method of claim [64] 66 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

71. The method of claim [68] 70 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

72. The method of claim [64] 66 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

73. The method of claim [70] 72 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

74. The method of claim [71] 73 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

75. The method of claim [64] 66 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

76. The method of claim [64] 66 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

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77. The method of claim [74] 76, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

78. The method of claim [73] 76, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

79. The method of claim [73] 76, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

80. The method of claim [73] 76, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

81. The method of claim [64] 66 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

82. The method of claim [79] 66 wherein the delivering is through at least one hollow needle.

83. The method of claim [64] 82 wherein the at least one hollow needle comprises an array of microneedles.

84. The method of claim [81] 82 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

85. The method of claim [64] 66 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

86. The method of claim [64] 66 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

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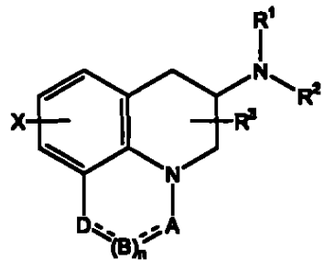
88. The method of claim [85] 87 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

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B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

89. The method of claim [86] 88 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

90. The method of claim [86] 88 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

91. The method of claim [85] 87 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

92. The method of claim [89] 91 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

93. The method of claim [85] 87 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

94. The method of claim [91] 93 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

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95. The method of claim [92] 94 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

96. The method of claim [85] 87 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

97. The method of claim [85] 87 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

98. The method of claim [95] 97, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

99. The method of claim [94] 97, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

100. The method of claim [94] 97, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

101. The method of claim [94] 97, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

102. The method of claim [85] 87 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

103. The method of claim [85] 87 wherein the delivering is through at least one hollow needle.

104. The method of claim [85] 103 wherein the at least one hollow needle comprises an array of microneedles.

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105. The method of claim [102] 103 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

106. The method of claim [85] 87 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

107. The method of claim [85] 87 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

REMARKS

Non-establishment of Opinion - Art. 17(2)(a) or (3):

The Examiner's statement asserts that the novelty, inventive step, and industrial applicability has not and will not be the subject of the International Preliminary Examination in respect of claims that have not been searched. According to the International Search Report (ISR), claims 1, 5-23, 27-45, 49-66, 70-87, and 91-107 allegedly relate to a compound that cannot be sufficiently characterized by its pharmacological effect. The ISR also asserted that the claims also lack clarity under Article 6 because an attempt is made to define a compound according to a result to be achieved.

Applicant respectfully disagrees. More particularly, the subject matter of the claims is not a compound. Applicant is not claiming the compound itself, and the claims do not cover "all compounds having this characteristic or property." Instead, the claims are directed to a method for systemic administration of a compound, not the compound itself. See Claims 1, 22, 44, 66, and 87.

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For these reasons, it is submitted that the claims do not so relate to a compound as to render them unsearchable, nor do they lack clarity under Article 6. Applicant therefore requests that a detailed substantive examination be performed on all claims.

If Applicant's request for a detailed substantive examination of all claims cannot be carried out for any reason, it is noted that the ISA stated that Claims 2-4, 24-26, 46-48, 67-69, and 88-90 were clear, supported and disclosed, and that the search has been carried out for these claims. Thus, it is requested that a detailed substantive examination be carried out for at least Claims 2-4, 24-26, 46-48, 67-69, and 88-90, inasmuch as the ISA itself asserts that these claims have been adequately searched.

Novelty and Inventive Step- Art. 33(1), (2) and (3) PCT:

Reconsideration is requested of the Examiner's reasoned statement under Rule 66.2(a)(ii) that some of the claims subject to an international search report do not appear to be novel and/or do not involve an inventive step, according to documents cited "X" and/or "Y" against the corresponding claims.

Applicant notes that there are three "X" references and no "Y" references in the international search report, all the remaining references being cited as "A" references defining the general state of the art and not being of particular relevance. Of the three "X" references, one (Brecht et al., WO 01 52854 A) has a publication date after the claimed priority date, and thus does not negate the novelty and inventive step of Applicant's present claims. (The other Brecht publication, WO 01 13903 A, is discussed in this response.)

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With respect to Elan Pharaceuticals, Inc., WO 01/37882 (hereinafter "Elan"), the passages cited in the search report disclose that Fenoldopan is a dopamine agonist that can be administered by any route suitable to achieve the desired result, including intradermally and subcutaneously (the latter being the preferred administration, see page 7, lines 17-19), or incorporated into particles. The only sensible reading of page 8, lines 14-17 is that the entrapped drug is (1) either administered subcutaneously, generally as a bolus injection, or (2) as an alternative, as an intermittent infusion, typically from an intradermal or subcutaneous injection site, which, in case (2), achieves prolonged release of fenoldopam from the intradermal or subcutaneous injection site. There is simply no logically cohesive reading of the passage at page 8, lines 14-17 that supports or describes an intradermal bolus injection.

More specifically, if the alternatives at page 8, lines 14-17 are interpreted as being intradermal or subcutaneous bolus injection vs. intradermal or subcutaneous intermittent infusion, the initial phrase, "The entrapped drug is administered subcutaneously, generally as..." has to be considered either as being contradictory or superfluous. Moreover, a subcutaneous bolus injection would not "achieve prolonged release of fenoldopam from the injection site," whereas this type of release could be expected to be achieved via intermittent infusion from an intradermal or subcutaneous injection site.

Thus, it cannot be said that Elan teaches or suggests a dermal bolus injection or any other injection of a hydrophobic dopamine agonist to the dermis of a mammal, wherein improved systemic absorption is produced as compared to

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absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

By contrast, Applicant's Claim 1, as currently pending, recites "A method ... comprising delivering the dopamine agonist to the dermis of the mammal, wherein improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection." There is nothing taught or suggested in the cited passages of Elan or elsewhere in that reference regarding such a method. More specifically, there is nothing that would render the step of delivering a dopamine agonist to the dermis of an animal with improved systemic absorption relative to a bolus subcutaneous injection. See Applicant's disclosure at, for example, paragraphs 0018, 0019, 0038, and elsewhere. Moreover, Applicant's dependent claims 7 and 10 explicitly recite that delivery to the dermis is, respectively, by bolus injection or by repeated bolus injection. See, for example, paragraphs 0013, 0023, 0051, 0062 of Applicant's application.

For the above reasons, it is submitted that independent Claim 1 and Claims 2-21 (which are each dependent upon Claim 1) are novel over Elan and incorporate inventive steps that are not shown or suggested by Elan.

Claim 22 recites "... administration of a hydrophobic dopamine agonist to a mammal ... comprising selectively delivering the dopamine agonist to the dermis of the mammal ...". Elan, by contrast, teaches either a subcutaneous administration (see page 7, lines 17-19) or the incorporation of the agonist into particles, such as polymer particles or liposomes (see page 8, lines 13-14). It is submitted that the incorporation of the dopamine agonist into polymer particles or liposomes results in a hydrophillic composition for the dopamine agonist rather than a hydrophobic composition. In

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particular, it is submitted that the polymer particle examples cited by Elan (polyvinyl alcohol, polyvinylpyrrolidone, polyacrylic acid, and celluloses) are all soluble, hydrophillic compounds, as are liposomes. (See page 8, lines 18-22, and U.S. Patent No. 4,235,871, which is enclosed with this letter).

It is therefore submitted that Claim 22 incorporates novelty and inventive steps beyond those taught or suggested by Elan.

Claim 23 is dependent upon Claim 22, and additionally incorporates the improved systemic absorption feature of Claim 1 that is discussed above. Therefore, Claim 23 is both novel and inventive over Elan for the same reasons given with respect to both Claims 1 and 22 above.

Claims 24-43 are each dependent, directly or indirectly, upon both Claims 22 and 23, and are thus novel and inventive for at least the same reasons given above for Claims 22 and 23.

Claim 44 is similar to Claim 22, except that the systemic absorption from the dermis is explicitly claimed. It is thus submitted that Claim 44 is novel and incorporates an inventive step over Elan for reasons similar to that given with respect to Claim 22.

Claim 45 recites a novel feature similar to that recited by Claim 23, and is novel and inventive over Elan for similar reasons.

Various claims herein have been amended to correct a typographical error in its dependency. As herein amended, Claims 46-65 are directly or indirectly dependent upon Claims 44 and 45, and are thus novel and inventive over Elan for at least the same reasons.

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Claim 66 is similar to Claim 1, but more specifically recites specific conditions as to higher bioavailability, and/or other parameters compared to bolus subcutaneous administration of the dopamine agonist. Thus, Claim 66 is novel and inventive over Elan for reasons similar to that given above with respect to Claim 1.

Claims 67-86 are directly or indirectly dependent upon Claim 66 and are thus novel and inventive over Elan for the same reasons given with respect to Claim 66.

Claim 87 is similar to Claim 66, except that the result of the administration is explicitly claimed. Thus, Claim 87 is novel and inventive over Elan for substantially the same reasons given with respect to Claim 66.

Claims 88-107 are indirectly or directly dependent upon Claim 87 and are thus novel and inventive over Elan for the same reasons given with respect to Claim 87.

With respect to WO 01 13903 ("Brecht"), this reference recites a treatment for Restless Leg Syndrome that comprises administering both an $\alpha 2$-agonist and another neuropsychic drug. The cited passages recite specific dopamine agonists (see page 4, paragraph 4), which can be combined with other substances and administered by various methods, including via oral and transdermal preparations (see page 4 last paragraph to page 5, paragraph 2). A transdermal plaster may be used that releases the active substance continuously into the skin (see page 4 to page 6, paragraph 1). However, there is no teaching or suggestion of administering a hydrophobic dopamine agonist to a mammal, wherein improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

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More particularly, hydrophobic substances have been intradermally administered locally or injected at a slow rate (see Applicant's application at paragraph 0009 and 0011). Water soluble substances have been administered intradermally, as well (see paragraph 0010). However, improved absorption compared to subcutaneous administration has not been demonstrated, nor is there any teaching or suggestion of such in Brecht. With continuous slow administration, as is described in Brecht (see page 6 of Brecht), one would never notice relatively poor absorption because the rate limiting factor is the rate of delivery. Only when the dopamine agonist is delivered rapidly by bolus administration is the rate of absorption limited by dermal absorption.

Applicant's invention relates to the fact that, when a hydrophobic dopamine agonist is administered intradermally, it is well absorbed whether administered rapidly (bolus) or slowly (infusion). By challenging a system with rapid administration (bolus), intradermal absorption is revealed to be better than by subcutaneous bolus injection. No such administration is shown or suggested by Brecht.

By contrast, Applicant's Claim 1, as currently pending, recites "A method ... comprising delivering the dopamine agonist to the dermis of the mammal, wherein improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection." There is nothing taught or suggested in the cited passages of Brecht or elsewhere in that reference regarding such a method. More specifically, there is nothing that would render the step of delivering a dopamine agonist to the dermis of an animal with improved systemic absorption relative to a bolus subcutaneous injection. See Applicant's

disclosure at, for example, paragraphs 0018, 0019, 0038, and elsewhere. Moreover, Applicant's dependent claims 7 and 10 explicitly recite that delivery to the dermis is, respectively, by bolus injection or by repeated bolus injection. See, for example, paragraphs 0013, 0023, 0051, 0062 of Applicant's application.

For the above reasons, it is submitted that independent Claim 1 and Claims 2-21 (which are each dependent upon Claim 1) are novel over Brecht and incorporate inventive steps that are not shown or suggested by Brecht.

Claim 22 recites "... administration of a hydrophobic dopamine agonist to a mammal ... comprising selectively delivering the dopamine agonist to the dermis of the mammal ...". Brecht, by contrast, teaches either a subcutaneous administration (see page 7, lines 17-19) or the incorporation of the agonist into particles, such as polymer particles or liposomes (see page 8, lines 13-14). It is submitted that the incorporation of the dopamine agonist into polymer particles or liposomes results in a hydrophillic composition for the dopamine agonist rather than a hydrophobic composition. In particular, it is submitted that the polymer particle examples cited by Brecht (polyvinyl alcohol, polyvinylpyrrolidone, polyacrylic acid, and celluloses) are all soluble, hydrophillic compounds, as are liposomes. (See page 8, lines 18-22, and U.S. Patent No. 4,235,871, which is enclosed with this letter).

It is therefore submitted that Claim 22 incorporates novelty and inventive steps beyond those taught or suggested by Brecht.

Claim 23 is dependent upon Claim 22, and additionally incorporates the improved systemic absorption feature of Claim 1 that is discussed above. Therefore, Claim 23 is both novel and inventive over Brecht for the same reasons given with respect to both Claims 1 and 22 above.

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Claims 24-43 are each dependent, directly or indirectly, upon both Claims 22 and 23, and are thus novel and inventive for at least the same reasons given above for Claims 22 and 23.

Claim 44 is similar to Claim 22, except that the systemic absorption from the dermis is explicitly claimed. It is thus submitted that Claim 44 is novel and incorporates an inventive step over Brecht for reasons similar to that given with respect to Claim 22.

Claim 45 recites a novel feature similar to that recited by Claim 23, and is novel and inventive over Brecht for similar reasons.

Various claims herein have been amended to correct a typographical error in its dependency. As herein amended, Claims 46-65 are directly or indirectly dependent upon Claims 44 and 45, and are thus novel and inventive over Brecht for at least the same reasons.

Claim 66 is similar to Claim 1, but more specifically recites specific conditions as to higher bioavailability, and/or other parameters compared to bolus subcutaneous administration of the dopamine agonist. Thus, Claim 66 is novel and inventive over Brecht for reasons similar to that given above with respect to Claim 1.

Claims 67-86 are directly or indirectly dependent upon Claim 66 and are thus novel and inventive over Brecht for the same reasons given with respect to Claim 66.

Claim 87 is similar to Claim 66, except that the result of the administration is explicitly claimed. Thus, Claim 87 is novel and inventive over Brecht for substantially the same reasons given with respect to Claim 66.

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Claims 88-107 are indirectly or directly dependent upon Claim 87 and are thus novel and inventive over Brecht for the same reasons given with respect to Claim 87.

For the above reasons, it is respectfully requested that a detailed international preliminary examination report be issued indicating that the claims as herein amended are novel, involve an inventive step, and have industrial applicability.

Respectfully submitted,

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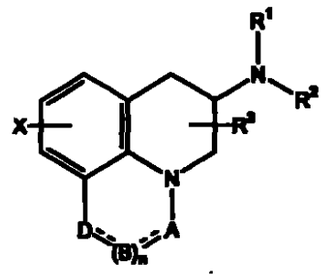
WHAT IS CLAIMED IS:

1. A method for systemic administration of a hydrophobic dopamine agonist to a mammal, the method comprising delivering the dopamine agonist to the dermis of the mammal, wherein improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

2. The method of claim 1 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "---" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

3. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

4. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

5. The method of claim 1 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

6. The method of claim 5 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

7. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

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8. The method of claim 7 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

9. The method of claim 8 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

10. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

11. The method of claim 1 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

12. The method of claim 11, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

13. The method of claim 11, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

14. The method of claim 11, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

15. The method of claim 11, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

16. The method of claim 1 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

17. The method of claim 16 wherein the delivering is through at least one hollow needle.

18. The method of claim 17 wherein the at least one hollow needle comprises an array of microneedles.

19. The method of claim 18 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

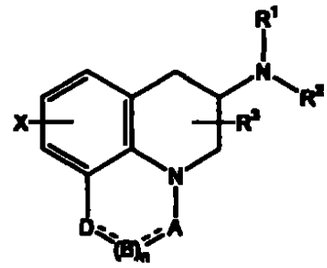
20. The method of claim 1 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

21. The method of claim 1 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

22. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal to obtain systemic absorption of the dopamine agonist from the dermis.

23. The method of claim 22 wherein improved systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

24. The method of claim 23 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as

above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ---- is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

25. The method of claim 24 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

26. The method of claim 24 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

27. The method of claim 23 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

28. The method of claim 27 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

29. The method of claim 23 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

30. The method of claim 29 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

31. The method of claim 30 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

32. The method of claim 23 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

33. The method of claim 23 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

34. The method of claim 33, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

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35. The method of claim 33, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

36. The method of claim 33, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

37. The method of claim 33, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

38. The method of claim 23 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

39. The method of claim 23 wherein the delivering is through at least one hollow needle.

40. The method of claim 39 wherein the at least one hollow needle comprises an array of microneedles.

41. The method of claim 39 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

42. The method of claim 23 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

43. The method of claim 23 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

44. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal wherein systemic absorption of the dopamine agonist from the dermis is obtained.

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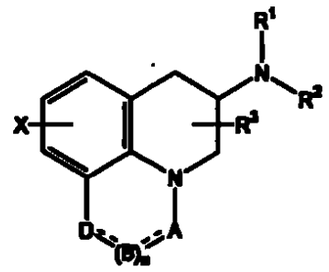
45. The method of claim 44 wherein improved systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

46. The method of claim 45 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ---- is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

47. The method of claim 46 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

48. The method of claim 46 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

49. The method of claim 45 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

50. The method of claim 49 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

51. The method of claim 45 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

52. The method of claim 51 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

53. The method of claim 52 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

54. The method of claim 45 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

55. The method of claim 45 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

56. The method of claim 55, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

57. The method of claim 55, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

58. The method of claim 55, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

59. The method of claim 55, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

60. The method of claim 45 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

61. The method of claim 45 wherein the delivering is through at least one hollow needle.

62. The method of claim 61 wherein the at least one hollow needle comprises an array of microneedles.

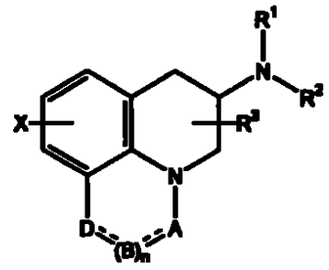
63. The method of claim 61 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Bellevi61lle spring, iontophoresis, or sonophoresis.

64. The method of claim 45 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater. .

65. The method of claim 45 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

66. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal to achieve a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag}, and/or a substantially greater K_a as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

67. The method of claim 66 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ⎓ is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

68. The method of claim 67 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

69. The method of claim 67 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

70. The method of claim 66 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

71. The method of claim 70 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

72. The method of claim 66 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

73. The method of claim 72 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

74. The method of claim 73 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

75. The method of claim 66 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

76. The method of claim 66 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

77. The method of claim 76, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

78. The method of claim 76, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

79. The method of claim 76, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

80. The method of claim 76, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

81. The method of claim 66 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

82. The method of claim 66 wherein the delivering is through at least one hollow needle.

83. The method of claim 82 wherein the at least one hollow needle comprises an array of microneedles.

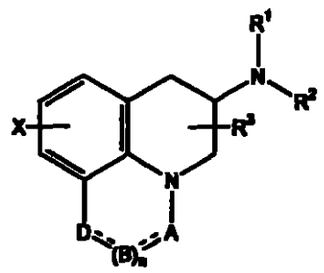
84. The method of claim 82 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

85. The method of claim 66 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

86. The method of claim 66 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

87. A method for administration of a hydrophobic dopamine agonist to a mammal, the method comprising selectively delivering the dopamine agonist to the dermis of the mammal wherein a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag}, and/or a substantially greater K_a is produced as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

88. The method of claim 87 wherein the dopamine agonist is as set forth in formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ⎯ is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-

CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

89. The method of claim 88 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

90. The method of claim 88 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

91. The method of claim 87 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

92. The method of claim 91 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

93. The method of claim 87 wherein the hydrophobic dopamine agonist is delivered to the dermis by bolus injection.

94. The method of claim 93 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

95. The method of claim 94 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

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96. The method of claim 87 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

97. The method of claim 87 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

98. The method of claim 97, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

99. The method of claim 97, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

100. The method of claim 97, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

101. The method of claim 97, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

102. The method of claim 87 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

103. The method of claim 87 wherein the delivering is through at least one hollow needle.

104. The method of claim 103 wherein the at least one hollow needle comprises an array of microneedles.

105. The method of claim 103 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

106. The method of claim 87 wherein the hydrophobic dopamine agonist has a logP of about 1.5 or greater.

107. The method of claim 87 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

6794S-023003/PC ATENT COOPERATI N TR CTY

3 month response due 9/24/03

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Holland, Donald R.
HARNESS, DICKEY & PIERCE P.L.C.
7700 Bonhomme Avenue, Suite 400
St. Louis, Missouri 63105
ETATS-UNIS D'AMERIQUE

RECEIVED
JUN 25 2003
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing (day/month/year)	24.06.2003
Applicant's or agent's file reference: 6794S-023POB	REPLY DUE: within 3 month(s) from the above date of mailing

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/19918	24/06/2002	29/06/2001

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

A61M5/158

Applicant

PHARMACIA CORPORATION

1. This written opinion is the second drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29/10/2003.

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized officer / Examiner
Martin, E

Formalities officer (incl. extension of time limits)
Cardenas, C
Telephone No. +31 70 340 3370

I. Basis of the opinion

1. With regard to the elements of the international application (Replacement *sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, pages:

1-32 as originally filed

Claims, No.:

1-107 as received on 03/04/2003 with letter of 01/04/2003

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

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

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-107 (all in part),

because:

   ☒ the said international application, or the said claims Nos. 1-107, with regard to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-107 (all in part) are so unclear that no meaningful opinion could be formed (*specify*):
   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

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

1. Statement

Novelty (N)	Claims	1-107
Inventive step (IS)	Claims	1-107
Industrial applicability (IA)	Claims	1-107

2. Citations and explanations
see separate sheet

Re Item III

1. Claims 1-107 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Claims 1-107 (all in part) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not defined.

2.1 Claims 1-107 attempt to define the subject-matter in terms of the result to be achieved, namely "improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection", or "selectively delivering the dopamine agonist to the dermis", or "a substantially higher bioavailability and/or a substantially higher C_{max}, and/or a substantially higher T_{max}, and/or a substantially shorter T_{lag}, and/or a substantially greater K_a, as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose". These features do not provide instructions which are sufficiently clear for an expert to reduce them to practice without undue burden.

The description does not specify the experimental methods and conditions under which comparison with the bolus subcutaneous administration should be performed, furthermore no tests are specified by which the results of the comparison with the bolus subcutaneous administration, or the selective delivery to the dermis, can be verified directly and positively. The method of intradermal administration, the method of subcutaneous administration, the species, the subjects, the number of subjects, the experimental design of the studies, the assay methods, the conditions of the studies, and the method of calculation of parameters are not specified. For the parameters T_{max}, C_{max}, T_{lag}, it is not specified if they are determined in blood, plasma, urine or other body fluids. For the parameter of bioavailability it is not specified if relative or absolute bioavailability is meant. Moreover, the definition of the bioavailability given on page 7, paragraph 18 of the description is not according to the generally used definition, because the calculation is not based on the dosage and AUC (or clearance), of an intravenous dosis and an extravascular dosis, nor is the proviso made that the clearance should remain constant.

Furthermore, the term "improved" used in claims 1, 11, 23, 33, 45, 55, 76 and 97 is vague and unclear. It is not clear whether the term "improved" means an increase or a decrease, or both. This term leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

The definitions of the parameters, the reference bolus subcutaneous administration, the selective delivery, and the term "improved" are therefore unclear and ambiguous, thus rendering the scope of the claimed subject-matter unclear (Article 6 PCT), and furthermore lack sufficient disclosure in the description (Article 5 PCT). Consequently, the desired technical effects as specified in said claims 1-107 cannot be verified by experimentation and thus do not constitute a testable criterion.

Moreover, the following functional statement used in claims 1, 5-23, 27-45, 49-66, 70-87, 91-107 does not enable the skilled person to determine which technical features are necessary to perform the stated function: "hydrophobic dopamine agonist". The feature "dopamine agonist" does not provide instructions which are sufficiently clear for an expert to reduce them to practice without undue burden. The result is not one which can be verified directly and positively by tests adequately specified in the description. Moreover, the term "hydrophobic" is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

2.2 The international search report has not been established for part of the claims 1-107.

2.3 Consequently the examination has only been carried out for those part of the claims which appear to be clear, supported and disclosed (Article 34(4)(a)(ii) PCT).

Re Item V

1. Reference is made to the following documents:

D1: WO 01 37882 A (ELAN PHARM INC) 31 May 2001 (2001-05-31)
D2: WO 01 13903 A (BOEHRINGER INGELHEIM PHARMA ;BRECHT HANS MICHAEL (DE)) 1 March 2001 (2001-03-01)

2. Novelty and inventive step

Furthermore, as far as the application can be clearly understood, the subject-matter of independent claims 1, 22, 44, 66, 87 is not new in the sense of Article 33(2) PCT. The subject-matter of claims 1, 22, 44, 66 and 87 is understood to concern a method for systemic administration of a hydrophobic dopamine agonist to a mammal, the method comprising delivering the dopamine agonist to the dermis of the mammal.

The document D1 discloses (the references in parentheses applying to this document): intradermal administration of the hydrophobic dopamine agonist fenoldopam (see page 2, lines 25-24, page 7, lines 13-16, and page 8, lines 13-17. The subject-matter of independent claims 1, 22, 44, 66, and 87 is therefore not new Article 33(2) PCT.

The document D2 discloses (the references in parentheses applying to this document): a transdermal plaster with the dopamine agonist (R)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-one (see page 4, paragraph 4, page 4, last paragraph - page 5, paragraph 2, page 5, last paragraph - page 6, paragraph 1, claims 1, 11, 12, 25 and 26). Transdermal administration is understood as being a method for selectively delivering a compound to the dermis. The subject-matter of independent claims 1, 22, 44, 66, and 87 is therefore not new Article 33(2) PCT.

It should be noted that subject-matter that is not novel, cannot be considered to be inventive either. Therefore, the subject-matter of independent claims 1, 22, 44, 66, and 87 does not involve an inventive step in the sense of Article 33(3) PCT.

Dependent claims 2-21, 23-43, 45-65, 67-86, 88-107 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to novelty and/or inventive step (Articles 33(2) and 33(3) PCT). The reasons therefor are that the additional features of the said claims are either directly known from documents D1 and D2, or are a combination of features obvious to the man skilled in the art in consideration of the disclosure of the prior art named in the present proceedings, or they concern only minor modifications which lie within the normal practice of the man skilled in the art.

3. For the assessment of the present claims 1-107 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Further remarks

The embodiment of the invention described in example 1 and shown in table 4 does not fall within the scope of the claims. The C_{max}, T_{max} and AUC of intradermal administration do not appear to be significantly different from the C_{max}, T_{max} and AUC of a subcutaneous bolus injection. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).

IN THE EUROPEAN PATENT OFFICE
AS INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

International Application No.:	PCT/US02/19918
International Filing Date:	24 June 2002
Applicant:	Pharmacia Corporation
Title:	ENHANCED PHARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS (title as established by the Authority)
Attorney Docket:	6794S-000023POB

European Patent Office
IPEA
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
NETHERLANDS

AMENDMENT AND REPLY TO WRITTEN OPINION UNDER RULE 66 PCT

This paper is submitted in response the IPEA's written opinion dated June 24, 2003, and it is accompanied by replacement sheets 33-51 submitted herewith. A previous set of claim amendments were submitted on 1 April 2003

Claim Amendments Under Rule 66.3 PCT:

Claims 1, 20, 22, 23, 42, 44, 45, 64, 66, 85, 87 and 106 are amended, and Claims 7, 29, 51, 72 and 93 are cancelled without prejudice or disclaimer in this paper. Claims 2-6 are unchanged. The changes made to the amended claims are indicated below. Deletions are shown by ~~strikeout typeface~~ or by [[double bracketing]] and additions are shown by underscoring.

Please cancel claims 7, 29, 51, 72 and 93, and amend claims 1, 20, 22, 23, 42, 44, 45, 64, 66, 85, 87 and 106 as shown below.

1. A method for systemic administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising delivering the dopamine agonist by bolus injection to the dermis of the mammal, wherein ~~improved~~ increased systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

20. The method of claim 1 wherein the hydrophobic dopamine agonist has a logP of about [[1.5]] 2.0 or greater.

22. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal to obtain systemic absorption of the dopamine agonist from the dermis.

23. The method of claim 22 wherein ~~improved~~ increased systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis by bolus injection as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

42. The method of claim 23 wherein the hydrophobic dopamine agonist has a logP of about [[1.5]] 2.0 or greater.

44. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal wherein systemic absorption of the dopamine agonist from the dermis is obtained.

45. The method of claim 44 wherein ~~improved~~ increased systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist by bolus injection to the dermis as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

64. The method of claim 45 wherein the hydrophobic dopamine agonist has a logP of about ~~1.5~~ 2.0 or greater.

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66. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal to achieve a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag} and/or a substantially greater K_a as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

85. The method of claim 66 wherein the hydrophobic dopamine agonist has a logP of about [[1.5]] 2.0 or greater.

87. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal wherein a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag} and/or a substantially greater K_a is produced as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

106. The method of claim 87 wherein the hydrophobic dopamine agonist has a logP of about [[1.5]] 2.0 or greater.

Remarks

Support for the subject matter of the amended claims will be found in the corresponding claims of the original application, as set forth in the above table. Additional support can be found as follows. Support for "delivering the dopamine agonist by bolus injection to the dermis" as recited in claims 1, 22, 23, 44, 45, 66 and 87 as amended can be found at least on claims 7, 29, 51, 72 and 93 as originally filed. Support for "increased systemic absorption" as recited in claims 1, 23 and 45 as amended can be found at least on paragraph 50, final sentence (page 23, lines 29-31).

Support for "a hydrophobic dopamine agonist having a logP of about 1.5 or greater" as recited in claims 1, 22 and 44 as amended can be found at least on claims 20, 42, 64 and 85 as originally filed. Support for "the hydrophobic dopamine agonist has a logP of about 2.0 or greater" in claims 20, 42, 64, 85 and 106 as amended can be found at least on paragraph 16 final sentence (page 6, lines 4-7).

Non-establishment of Opinion

The IPEA's statement asserts that Claims 1-107 relate to subject matter considered by the Authority to by covered by the provisions of Rule 67.1(iv) PCT, which is directed to methods for treatment of a human or animal, as well as diagnostic methods. Consequently, the Examiner offers no opinion with respect to the industrial applicability of the subject matter of the claims.

Applicant respectfully disagrees with the IPEA's conclusion that the claims are directed to methods for treatment. The claims recite neither a method of treatment, nor a diagnostic method. Rather, the claims are directed to methods for systemic administration of a dopamine agonist. Such methods are not inherently methods for treatment. Nor are they inherently diagnostic methods. Applicant, therefore, requests withdrawal of the assessment.

The IPEA's statement asserts that Claim 1-107 (all in part) do not meet the requirements of Article 6 PCT because the subject matter is not defined. In this regard, the IPEA asserts that the claims attempt to define their subject-matter in terms of results to be achieved, and do not provide instructions which are sufficiently clear for an expert to reduce them to practice without undue burden. In support this position, the IPEA cites the claim recitation "improved systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection," as well as other claim recitations. In order to address the IPEA's concerns, independent claims 1, 22, 44, 66 and 87 as well as

dependent claims 23 and 45 are amended in this paper with the addition of the recitation that delivering the dopamine agonist is "by bolus injection" as originally recited in dependent claims 7, 29, 51, 72, and 93.

The IPEA also asserts that the description does not specify the experimental methods and conditions under which comparisons should be made, citing a number of conditions including method of intradermal administration, the method of subcutaneous administration, the species, the subjects, the number of subjects, the experimental design of the studies, the assay methods, the conditions of the studies and the method of calculation of parameters. Applicant respectfully disagrees, because such conditions are identified in the specification, for example in paragraphs 40 and 41, and pharmacokinetic parameters are described at least on paragraphs 18-20. Applicant, therefore, requests reconsideration and withdrawal of the assessment.

The IPEA also asserts that the that the term "improved" as used in claims 1, 11, 23, 33, 45, 55, 76 and 97 is vague and unclear, because "improved" can mean an increase, a decrease, or both. Applicant respectfully disagrees, and requests reconsideration of the assessment, because both the specification and the claims make clear for each pharmacokinetic parameter whether "improved" refers to an increase or a decrease. For example, the specification, at least on page 7, paragraph 18 indicates that "improved systemic absorption can be measured by...increase in bioavailability, decrease in T_{max}, increase in C_{max}, decrease in T_{lag}...". Further descriptions of pharmacokinetic parameters are provided at least on paragraphs 18-20. In addition, claims such as dependent claims 11-14 (as amended) recite individual pharmacokinetic parameters, and indicate whether an "improved" value for the parameter involves an increase or a decrease in a parameter value. Therefore, the specification and claims leave no doubt whether "improved" refers to an increase or

decrease for any particular pharmacokinetic parameter. In addition, the recitation of "improved systemic absorption" has been amended to recite "increased systemic absorption" in independent claims 1and 22, and dependent claim 43 (as amended). Applicant, therefore, requests withdrawal of the assessment.

The IPEA also asserts that the that the term "hydrophobic dopamine agonist" as used in claims 1, 5-23, 27-45,49-66, 70-87, and 91-107 is a functional statement that does not enable a skilled person to determine which technical features are necessary to perform the stated function. In support of this contention, the IPEA asserts that the recitation of "dopamine agonist" does not provide instructions which are sufficiently clear for an expert to reduce them to practice without undue burden. Applicant respectfully disagrees, as the term "dopamine agonist" is well understood in the art. For example, the NCBI database on the internet (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=PubMed) lists well over 2,000 references antedating the application filing date that include the phrase "dopamine agonist." Because the phrase "dopamine agonist" is well understood in the art, applicant asserts that one of skill in the art can recognize a dopamine agonist without undue burden. In addition, the IPEA asserts that the term "hydrophobic" is vague and unclear. However, independent claims reciting "hydrophobic dopamine agonist" now also recite "having a logP of about 1.5 or greater." Applicant believes this amendment addresses the IPEA's concerns, and, therefore, request reconsideration and withdrawal of the assessment.

Novelty and Inventive Step under Rule 66.2(a)(ii)

The IPEA asserts that the subject matter of claims 1, 22, 44, 66, and 87 are not new under the criteria of Article 33(2) PCT, in view of references D1 (Elan) and D2 (Boehringer Ingelheim). Applicant requests reconsideration of this assessment, because neither of these references teach the claimed subject matter in the present

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application. According to the IPEA, the D1 reference discloses intradermal administration of the fenoldopam. However, this reference fails to disclose bolus administration of a dopamine agonist to the dermis. Similarly, according to the IPEA, the D2 reference discloses a transdermal plaster with a dopamine agonist. Even if, *arguendo*, transdermal administration is understood to be a method for selective delivery of a compound to the dermis, this reference still does not teach bolus administration of a dopamine agonist to the dermis. Because neither the D1 reference nor the D2 reference, separately or in combination, teaches or suggests bolus administration of a dopamine agonist, these references do not negate either novelty or inventive step of the present invention. Applicant, therefore, requests withdrawal of the IPEA's assessment.

The IPEA also asserts that dependent claims 2-21, 23-43, 45-65, 67-86 and 88-107 do not appear to contain any additional features which meet the requirements of the PCT with respect to novelty and/or inventive step. Applicant believes this assessment to be obviated because the independent claims are novel.

Under "Further Remarks," the IPEA states that the invention described in example 1 and shown in table 4 does not fall within the scope of the claims. The IPEA asserts that the C_{max}, T_{max} and AUC of intradermal administration do not appear to be significantly different from the C_{max}, T_{max} and AUC of a subcutaneous bolus injection. However, there is no PCT rule that requires a showing of statistical significance for data falling within claim recitations of increased values. Nonetheless, it is indicated in the application that plasma levels following administration to the dermis compared to plasma levels following subcutaneous administration differed when analyzed by a Heterogeneity of Variance test (see page 30, paragraph 67).

For the above reasons, it is respectfully requested that the IPEA's statement of non-establishment of opinion with regard to novelty, inventive step, or to

industrially applicability under rule 67.1(iv) PCT be withdrawn, and that assertions of lack of novelty or inventive step under Article 33(2) PCT be withdrawn.

Respectfully submitted,

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Applicant:	Pharmacia Corporation
Title:	ENHANCED PHARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS (title as established by the Authority)
Attorney Docket:	6794S-000023/WO/POB

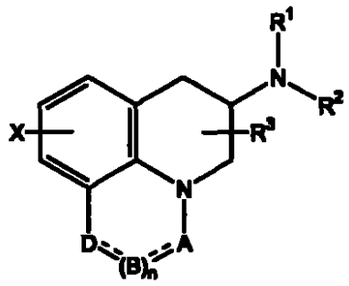
REPLACEMENT CLAIMS

(19 SHEETS)

WHAT IS CLAIMED IS:

1. A method for systemic administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising delivering the dopamine agonist by bolus injection to the dermis of the mammal, wherein increased systemic absorption is produced as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

2. The method of claim 1 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "---" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

3. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

4. The method of claim 2 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

5. The method of claim 1 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

6. The method of claim 5 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

7. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

8. The method of claim 7 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

9. The method of claim 1 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

10. The method of claim 1 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

11. The method of claim 10, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

12. The method of claim 10, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

13. The method of claim 10, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

14. The method of claim 10, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

15. The method of claim 1 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

16. The method of claim 15 wherein the delivering is through at least one hollow needle.

17. The method of claim 16 wherein the at least one hollow needle comprises an array of microneedles.

18. The method of claim 17 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

19. The method of claim 1 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

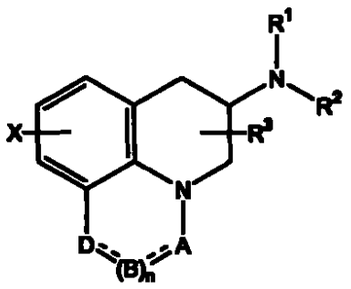
20. The method of claim 1 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

21. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal to obtain systemic absorption of the dopamine agonist from the dermis.

22. The method of claim 21 wherein increased systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist to the dermis by

bolus injection as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

23. The method of claim 22 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined

above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

24. The method of claim 23 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

25. The method of claim 23 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

26. The method of claim 22 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

27. The method of claim 26 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

28. The method of claim 22 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

29. The method of claim 28 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

30. The method of claim 22 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

31. The method of claim 22 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

32. The method of claim 31, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

33. The method of claim 31, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

34. The method of claim 31, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

35. The method of claim 31, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

36. The method of claim 22 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

37. The method of claim 22 wherein the delivering is through at least one hollow needle.

38. The method of claim 37 wherein the at least one hollow needle comprises an array of microneedles.

39. The method of claim 37 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

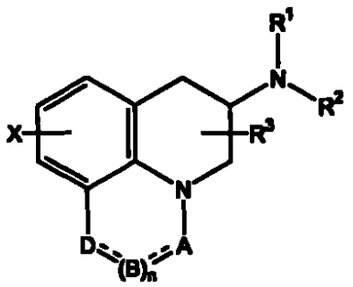
40. The method of claim 22 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

41. The method of claim 22 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

42. A method for administration of a hydrophobic dopamine agonist have a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal wherein systemic absorption of the dopamine agonist from the dermis is obtained.

43. The method of claim 42 wherein increased systemic absorption of the dopamine agonist is produced upon delivering the dopamine agonist by bolus injection to the dermis as compared to absorption produced upon delivering the dopamine agonist subcutaneously by bolus injection.

44. The method of claim 43 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, $N\text{-}CH_3$; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(4) when n is 1, and

A is CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, $N\text{-}CH_3$;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

45. The method of claim 44 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

46. The method of claim 44 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

47. The method of claim 43 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

48. The method of claim 47 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

49. The method of claim 43 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

50. The method of claim 49 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

51. The method of claim 43 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

52. The method of claim 43 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

53. The method of claim 52, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

54. The method of claim 52, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

55. The method of claim 52, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

56. The method of claim 52, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

57. The method of claim 43 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

58. The method of claim 43 wherein the delivering is through at least one hollow needle.

59. The method of claim 58 wherein the at least one hollow needle comprises an array of microneedles.

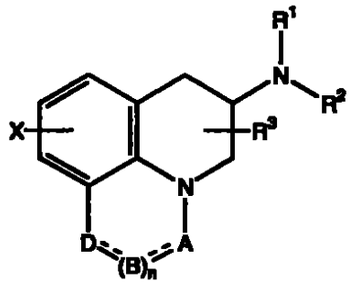
60. The method of claim 58 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Bellevi61lle spring, iontophoresis, or sonophoresis.

61. The method of claim 43 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

62. The method of claim 43 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

63. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal to achieve a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag}, and/or a substantially greater K_a as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

64. The method of claim 63 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl

substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH,

N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

65. The method of claim 64 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

66. The method of claim 64 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

67. The method of claim 63 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

68. The method of claim 67 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

69. The method of claim 63 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

70. The method of claim 69 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

71. The method of claim 63 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

72. The method of claim 63 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

73. The method of claim 72, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

74. The method of claim 72, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

75. The method of claim 72, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

76. The method of claim 72, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

77. The method of claim 63 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

78. The method of claim 63 wherein the delivering is through at least one hollow needle.

79. The method of claim 78 wherein the at least one hollow needle comprises an array of microneedles.

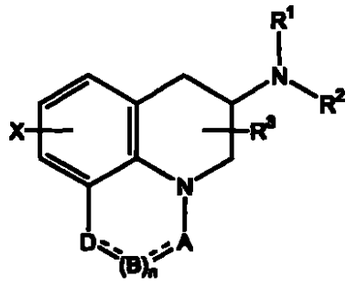
80. The method of claim 78 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

81. The method of claim 63 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

82. The method of claim 63 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

83. A method for administration of a hydrophobic dopamine agonist having a logP of about 1.5 or greater to a mammal, the method comprising selectively delivering the dopamine agonist by bolus injection to the dermis of the mammal wherein a substantially higher bioavailability and/or a substantially higher C_{max} and/or a substantially shorter T_{max} and/or a substantially shorter T_{lag} and/or a substantially greater K_a is produced as compared to that produced upon bolus subcutaneous administration of the dopamine agonist at an identical dose.

84. The method of claim 83 wherein the dopamine agonist is as set forth in formula (I):



(I) or pharmaceutically acceptable salts thereof, wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl or alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl or alkoxy, CN, carboxamide, carboxyl or

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(C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3, and n is 0 or 1; and

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where "----" is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH, N-CH_3;

(2) when n is 0, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N;

then

D is CH, N;

(3) when n is 1, and

A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH, SO_2; and

B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH, N-CH_3; then

D is CH_2, C=O, O, NH, N-CH_3;

(4) when n is 1, and

A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN, N; and

B is CH, N; then

D is CH_2, C=O, O, NH, N-CH_3;

(5) when n is 1, and

A is CH_2, $CHCH_3$, C=O, C=S, C=NH, SO_2, and

B is CH, N; then

D is CH, N; and pharmaceutically acceptable salts thereof to the human.

85. The method of claim 84 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione or a pharmaceutically acceptable salt thereof.

86. The method of claim 84 wherein the dopamine agonist is (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one or a pharmaceutically acceptable salt thereof.

87. The method of claim 83 wherein the bolus subcutaneous injection is delivered in not more than 10 minutes.

88. The method of claim 87 wherein the bolus subcutaneous injection is delivered in not more than 2 minutes.

89. The method of claim 83 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 10 minutes.

90. The method of claim 89 wherein the hydrophobic dopamine agonist is delivered to the dermis in not more than 2 minutes.

91. The method of claim 83 wherein the hydrophobic dopamine agonist is delivered to the dermis by repeated bolus injection.

92. The method of claim 83 wherein at least one pharmacokinetic parameter is improved upon delivery of the dopamine agonist to the dermis as compared to the same pharmacokinetic parameter upon delivering the dopamine agonist subcutaneously by bolus injection.

93. The method of claim 92, wherein the improved pharmacokinetic parameter comprises increased bioavailability of the dopamine agonist.

94. The method of claim 92, wherein the improved pharmacokinetic parameter comprises a decrease in T_{max}.

95. The method of claim 92, wherein the improved pharmacokinetic parameter comprises an increase in C_{max}.

96. The method of claim 92, wherein the improved pharmacokinetic parameter comprises a decrease in T_{lag}.

97. The method of claim 83 wherein the delivering is through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

98. The method of claim 83 wherein the delivering is through at least one hollow needle.

99. The method of claim 98 wherein the at least one hollow needle comprises an array of microneedles.

100. The method of claim 98 wherein the dopamine agonist is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

101. The method of claim 83 wherein the hydrophobic dopamine agonist has a logP of about 2.0 or greater.

102. The method of claim 83 wherein the dopamine agonist is in the form of nanoparticles or nanocrystals.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

HOLLAND, Donald, R.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, MO 63105
United States of America

Date of mailing (day/month/year) 16 September 2002 (16.09.02)	
Applicant's or agent's file reference 6794S-023POB	IMPORTANT NOTIFICATION
International application No. PCT/US02/19918	International filing date (day/month/year) 24 June 2002 (24.06.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 29 June 2001 (29.06.01)
Applicant PHARMACIA CORPORATION et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(a) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
29 June 2001 (29.06.01)	09/897,801	US	06 Augu 2002 (06.08.02)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Roberto PEREZ
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/304 (July 1998) 005109015

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PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

HOLLAND, Donald, R.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, MO 63105
United States of America

Date of mailing (day/month/year):
20 November 2003 (20.11.03)

Applicant's or agent's file reference
6784S-023POB

IMPORTANT NOTIFICATION

International application No.
PCT/US02/19918

International filing date (day/month/year)
24 June 2002 (24.06.02)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
PHARMACIA CORPORATION
Corporate Patent Department
800 North Lindbergh Blvd.,
Mail Zoria One
St. Louis, MO 63167
United States of America

State of Nationality: US
State of Residence: US
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
PHARMACIA CORPORATION
P.O. BOx 1027
Chesterfield, MO 63006
United States of America

State of Nationality: US
State of Residence: US
Telephone No.: 314-274-1000
Facsimile No.: 314-274-8085
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[X] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
Junko TAKEUCHI (Fax: 338 71 30)

Telephone No. (41-22) 338 8448

Form PCT/IB/308 (March 1994)

ASSIGNMENT

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Atty. Docket No. 6794S-000023/WO/POB

WHEREAS, the undersigned, hereinafter referred to collectively as Assignor, has invented:

ENHANCED PHARMACOKINETIC PROFILE OF HYDROPHOBIC DOPAMINE AGONISTS ADMINISTERED TO THE DERMIS

for which Assignor is about to make or has made United States or International application for patent

(a) ☐ executed on even date preparatory to filing (each inventor should sign this Assignment on the same day as he/she signs the Declaration and Power of Attorney);

(b) ☐ executed on _____, _____, _____; or

(c) ☒ filed on June 24, 2002, and assigned PCT International Application No. PCT/US02/19918;

(d) ☐ U.S. Patent No. _____, issued _____; and

WHEREAS, Pharmacia Corporation, 575 Maryville Centre Drive, St. Louis, Missouri 63141, hereinafter referred to as Assignee, is desirous of acquiring an interest therein:

NOW, THEREFORE, for good and valuable consideration, the receipt and adequacy whereof is hereby acknowledged, Assignor by these presents does sell, assign and transfer unto Assignee and its successors in interest, the full and exclusive right, title and interest in the United States of America and all foreign countries, including the right to claim priority under the laws of the United States, the Paris Convention, and any foreign countries, to the said invention as described in the aforesaid application, said application for patent and all Letters Patent therefor to be held and enjoyed by Assignee to the full end of the term for which said Letters Patent are granted and any extensions thereof as fully and entirely as the same would have been held by Assignor had this assignment and sale not been made, and the right to recover for past infringements of, or liabilities for, any of the rights relating to any of said applications or patents resulting therefrom;

Assignor hereby covenants and agrees to execute all instruments or documents required or requested for the making and prosecution of any applications of any type for patent in the United States and in all foreign countries including, but not limited to, any provisional, continuation, continuation-in-part, divisional, renewal or substitute thereof, and as to letters patent any reissue, re-examination, or extension thereof, and for litigation regarding, or for the purpose of protecting title and to the said invention, the United States application for patent, or Letters Patent therefor, and to testify in support thereof, for the benefit of Assignee without further or other compensation than that above set forth;

Assignor hereby covenants that no assignment, sale or agreement or encumbrance has been or will be entered into which would conflict with this Assignment; and

Assignor hereby requests the Commissioner of Patents and Trademarks to issue said Letters Patent of the United States of America to Assignee, and requests that any official of any country or countries foreign to the United States, whose duty it is to issue or grant patents and

ASSIGNMENT

applications as aforesaid, to issue said Letters Patent, Utility Model Registration or Inventor's Certificate to Assignee.

Assignor hereby authorizes and requests my attorney to insert here in parentheses (Application No. _____, filed _____) the filing date and application number of said application when known.

Thomas C. Pinkerton

State of Michigan)
) ss.
County of Kalamazoo)

On this 7th day of November, 2003, before me personally appeared the foregoing individual, who executed the foregoing instrument and who acknowledged to me that he executed the same of his own free will for the purpose therein set forth.

Debra J. Marquette
Notary Public,

(seal) Kalamazoo County, State of Michigan

My Commission Expires: DEBRA J. MARQUETTE
Notary Public, Kalamazoo County, MI
My Commission Expires 8/25/2004

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SUBSTITUTE CLAIMS

FOR COLOMBIA

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Substitute Claims

1. Use of a hydrophobic dopamine agonist having a logP of about 1.5 or greater for the production of a medicament for administration to the dermis of a mammal, wherein upon administration of the hydrophobic dopamine agonist, improved systemic absorption is produced relative to absorption produced upon injecting the hydrophobic dopamine agonist subcutaneously by bolus injection.

2. A device for administering to a mammal a hydrophobic dopamine agonist having a logP of about 1.5 or greater, the device being configured for administration of the hydrophobic dopamine agonist into the dermis to obtain systemic absorption of the hydrophobic dopamine agonist, wherein the device is an electroporation injection system or a thermal poration injection system.

3. A kit for administering to the dermis of a mammal, the kit comprising a hydrophobic dopamine agonist having a logP of about 1.5 or greater, wherein upon administration of the hydrophobic dopamine agonist to the dermis, improved systemic absorption is produced relative to absorption produced upon injecting the hydrophobic dopamine agonist subcutaneously.

4. The kit of claim 3, further comprising a device for administering the hydrophobic dopamine agonist to the mammal, the device being configured for administration of the hydrophobic dopamine agonist into the dermis to obtain systemic absorption of the hydrophobic dopamine agonist, wherein the device is an electroporation injection system or a thermal poration injection system.

5. The use of claim 1, wherein the administration is by bolus injection.

6. The use of claim 1, wherein at least one pharmacokinetic parameter is improved in the mammal, wherein the improved pharmacokinetic parameter is selected from the group consisting of an increase in bioavailability of the hydrophobic dopamine agonist, a decrease in T_{max}, an increase in C_{max}, and a decrease in T_{lag}.

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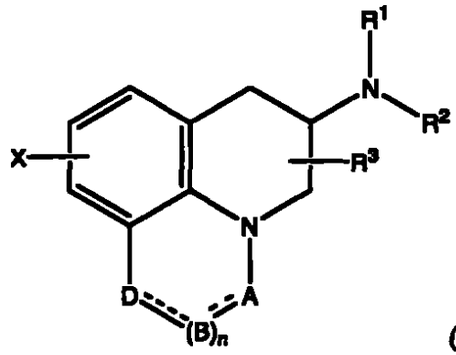
7. The use of claim 1, wherein the administering the hydrophobic dopamine agonist having a logP of about 1.5 or greater to the mammal comprises delivering the hydrophobic dopamine agonist through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

8. The use of claim 1, wherein the administering the hydrophobic dopamine agonist having a logP of about 1.5 or greater to the mammal comprises delivering the hydrophobic dopamine agonist through an array of microneedles.

9. The use of claim 1, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

10. The use of claim 1, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater has a logP of greater than 2.0.

11. The use of claim 1, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is as set forth in formula (I):



(I), wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl, C_{3-5} alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl, C_{1-6} alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3;

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ------ is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH or SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH or $N\text{-}CH_3$;

(2) when n is 0, and A is CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN or N;

then D is CH or N;

(3) when n is 1, and A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH or SO_2; and B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH or $N\text{-}CH_3$;

then D is CH_2, C=O, O, NH or $N\text{-}CH_3$;

(4) when n is 1, and A is CH, $C\text{-}SCH_3$, $C\text{-}NH_2$, $C\text{-}NHCH_3$, $C\text{-}NHCOOCH_3$, C-NHCN or N; and B is CH or N;

then D is CH_2, C=O, O, NH or $N\text{-}CH_3$;

(5) when n is 1, and A is CH_2, $CHCH_3$, C=O, C=S, C=NH or SO_2, and B is CH or N;

then D is CH or N;

and pharmaceutically acceptable salts thereof.

12. The use of claim 1, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is selected from the group consisting of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione, (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one, and pharmaceutically acceptable salts thereof.

13. The use of claim 1, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is in the form of nanoparticles or nanocrystals.

14. The device of claim 2, wherein the administration is by bolus injection.

15. The device of claim 2, wherein at least one pharmacokinetic parameter is improved in the mammal, wherein the improved pharmacokinetic parameter is selected from the group consisting of an increase in bioavailability of the hydrophobic dopamine agonist, a decrease in T_{max}, an increase in C_{max}, and a decrease in T_{lag}.

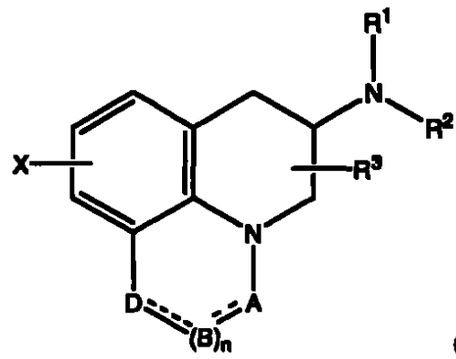
16. The device of claim 2, wherein the administering the hydrophobic dopamine agonist having a logP of about 1.5 or greater to the mammal comprises delivering the hydrophobic dopamine agonist through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

17. The device of claim 2, wherein the administering the hydrophobic dopamine agonist having a logP of about 1.5 or greater to the mammal comprises delivering the hydrophobic dopamine agonist through an array of microneedles.

18. The device of claim 2, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

19. The device of claim 2, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater has a logP of greater than 2.0.

20. The device of claim 2, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is as set forth in formula (I):



(I), wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl, C_{3-5} alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl, C_{1-6} alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3;

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ------ is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH or SO_2;

then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH or N-CH_3;

(2) when n is 0, and A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN or N;

then D is CH or N;

(3) when n is 1, and A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH or SO_2; and B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH or N-CH_3;

then D is CH_2, C=O, O, NH or N-CH_3;

(4) when n is 1, and A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN or N; and B is CH or N;

then D is CH_2, C=O, O, NH or N-CH_3;

(5) when n is 1, and A is CH_2, $CHCH_3$, C=O, C=S, C=NH or SO_2, and B is CH or N;

then D is CH or N;

and pharmaceutically acceptable salts thereof.

21. The device of claim 2, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is selected from the group consisting of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione, (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one, and pharmaceutically acceptable salts thereof.

22. The device of claim 2, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is in the form of nanoparticles or nanocrystals.

23. The kit as in claim 3 or 4, wherein the administration is by bolus injection.

24. The kit as in claim 3 or 4, wherein at least one pharmacokinetic parameter is improved in the mammal, wherein the improved pharmacokinetic parameter is selected from the group consisting of an increase in bioavailability of the hydrophobic dopamine agonist, a decrease in T_{max}, an increase in C_{max}, and a decrease in T_{lag}.

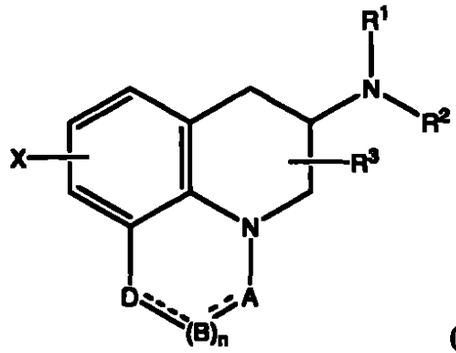
25. The kit as in claim 3 or 4, wherein the administering the hydrophobic dopamine agonist having a logP of about 1.5 or greater to the mammal comprises delivering the hydrophobic dopamine agonist through a cutaneous micropore created by any solid projection, electromotive force, thermal energy or gas ballistics.

26. The kit as in claim 3 or 4, wherein the administering the hydrophobic dopamine agonist having a logP of about 1.5 or greater to the mammal comprises delivering the hydrophobic dopamine agonist through an array of microneedles.

27. The kit as in claim 3 or 4, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is delivered by infusion pump, piezoelectric pump, electromotive pump, electromagnetic pump, Belleville spring, iontophoresis, or sonophoresis.

28. The kit as in claim 3 or 4, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater has a logP of greater than 2.0.

29. The kit as in claim 3 or 4, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is as set forth in formula (I):



(I), wherein

R^1, R^2 and R^3 are the same or different and are H, C_{1-6} alkyl (optionally phenyl substituted), C_{3-5} alkenyl, C_{3-5} alkynyl or C_{3-10} cycloalkyl, or where R^3 is as above and R^1 and R^2 are cyclized with the attached N atom to form pyrrolidinyl, piperidinyl, morpholinyl, 4-methylpiperazinyl or imidazolyl groups;

X is H, F, Cl, Br, I, OH, C_{1-6} alkyl, C_{1-6} alkoxy, CN, carboxamide, carboxyl or (C_{1-6} alkyl)carbonyl;

A is CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 or N;

B is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH or NCH_3;

D is CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH or NCH_3; and n is 0 or 1, and where ------ is a single or double bond,

with the provisos that:

(1) when n is 0, and A is CH_2, CH-(halogen) where halogen is defined above, $CHCH_3$, C=O, C=S, C=NH or SO_2;

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then D is CH_2, CH-(halogen) where halogen is as defined above, C=O, O, NH or N-CH_3;

(2) when n is 0, and A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN or N;

then D is CH or N;

(3) when n is 1, and A is CH_2, CH-(halogen) where halogen is as defined above, $CHCH_3$, C=O, C=S, C=NH or SO_2; and B is CH_2, CH-(halogen) where halogen is as defined above, C=O, NH or N-CH_3;

then D is CH_2, C=O, O, NH or N-CH_3;

(4) when n is 1, and A is CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN or N; and B is CH or N;

then D is CH_2, C=O, O, NH or N-CH_3;

(5) when n is 1, and A is CH_2, $CHCH_3$, C=O, C=S, C=NH or SO_2, and B is CH or N;

then D is CH or N;

and pharmaceutically acceptable salts thereof.

30. The kit as in claim 3 or 4, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is selected from the group consisting of (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinoline-2(1H)-thione, (*R*)-5,6-dihydro-5-(methylamino)-4H-imidazo[4,5-*ij*]-quinolin-2(1H)-one, and pharmaceutically acceptable salts thereof.

31. The kit as in claim 3 or 4, wherein the hydrophobic dopamine agonist having a logP of about 1.5 or greater is in the form of nanoparticles or nanocrystals.

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NOVEDAD DE LA INVENCION

REIVINDICACIONES

1.- El uso de un agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, en la producción de un medicamento para administración a la dermis de un mamífero, en donde tras la administración del agonista de dopamina hidrofóbico, se logra absorción sistémica mejorada respecto a la absorción obtenida después de inyectar el agonista de dopamina hidrofóbico subcutáneamente mediante inyección de bolo.

2.- Un dispositivo para administrar a un mamífero un agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más, caracterizado porque el dispositivo está configurado para la administración del agonista de dopamina hidrofóbico en la dermis para obtener absorción sistémica del agonista de dopamina hidrofóbico, en donde el dispositivo es un sistema de inyección por electroporación o un sistema de inyección por poración térmica.

3.- Un equipo para administración a la dermis de un mamífero, el equipo caracterizado porque comprende un agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, en donde tras la administración del agonista de dopamina hidrofóbico a la dermis, se logra absorción sistémica mejorada respecto a la absorción obtenida después de inyectar subcutáneamente el agonista de dopamina hidrofóbico.

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4.- El equipo de conformidad con la reivindicación 3, caracterizado además porque comprende un dispositivo para administrar el agonista de dopamina hidrofóbico al mamífero, el dispositivo estando configurado para administrar el agonista de dopamina hidrofóbico en la dermis para lograr absorción sistémica del agonista de dopamina hidrofóbico, en donde el dispositivo es un sistema de inyección por electroporación o un sistema de inyección por poración térmica.

5.- El uso como se reclama en la reivindicación 1, en donde la administración es mediante inyección de bolo.

6.- El uso como se reclama en la reivindicación 1, en donde se mejora por lo menos un parámetro farmacocinético en el mamífero, en donde el parámetro farmacocinético mejorado se selecciona del grupo que consiste de un incremento en biodisponibilidad del agonista de dopamina hidrofóbico, una disminución en $T_{máx}$, un incremento en $C_{máx}$ y una disminución en T_{lag}.

7.- El uso como se reclama en la reivindicación 1, en donde la administración del agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más al mamífero, comprende liberar el agonista de dopamina hidrofóbico a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

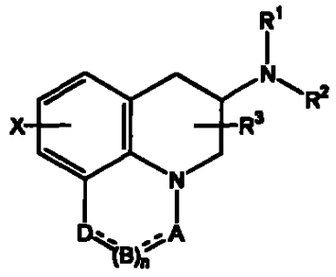
8.- El uso como se reclama en la reivindicación 1, en donde la administración del agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más al mamífero, comprende liberar el agonista de

dopamina hidrofóbico a través de una disposición de microagujas.

9.- El uso como se reclama en la reivindicación 1, en donde el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

10.- El uso como se reclama en la reivindicación 1, en donde el agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más, tiene un logP mayor de 2.0.

11.- El uso como se reclama en la reivindicación 1, en donde el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, es como se describe en la fórmula (I):



(I)

en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de

C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ═ es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo.

12.- El uso como se reclama en la reivindicación 1, en donde el agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más, se selecciona del grupo que consiste de (R)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, (R)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona, y sales farmacéuticamente aceptables de

los mismos.

13.- El uso como se reclama en la reivindicación 1, en donde el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, está en forma de nanopartículas o nanocristales.

14.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque la administración es mediante inyección de bolo.

15.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque se mejora por lo menos un parámetro farmacocinético en el mamífero, en donde el parámetro farmacocinético mejorado se selecciona del grupo que consiste de un incremento en biodisponibilidad del agonista de dopamina hidrofóbico, una disminución en $T_{máx}$, un incremento en $C_{máx}$ y una disminución en T_{lag}.

16.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque la administración del agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más al mamífero, comprende liberar el agonista de dopamina hidrofóbico a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

17.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque la administración del agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más al mamífero, comprende liberar el agonista de dopamina hidrofóbico a través de una

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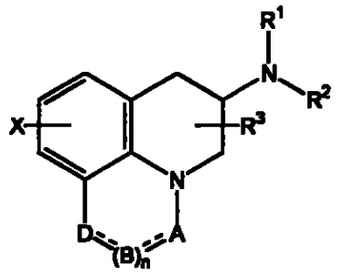
disposición de microagujas.

18.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

19.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más, tiene un logP mayor de 2.0.

20.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, es como se describe en la fórmula (I):



(I)

en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I, OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de

C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ═══ es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo.

21.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más, se selecciona del grupo que consiste de (R)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona, (R)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona, y sales

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farmacéuticamente aceptables de los mismos.

22.- El dispositivo de conformidad con la reivindicación 2, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, está en forma de nanopartículas o nanocristales.

23.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque la administración es mediante inyección de bolo.

24.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque se mejora por lo menos un parámetro farmacocinético en el mamífero, en donde el parámetro farmacocinético mejorado se selecciona del grupo que consiste de un incremento en biodisponibilidad del agonista de dopamina hidrofóbico, una disminución en $T_{máx}$, un incremento en $C_{máx}$ y una disminución en T_{lag}.

25.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque la administración del agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más al mamífero, comprende liberar el agonista de dopamina hidrofóbico a través de un microporo cutáneo creado mediante cualquier proyección de sólidos, fuerza electromotriz, energía térmica o balística de gases.

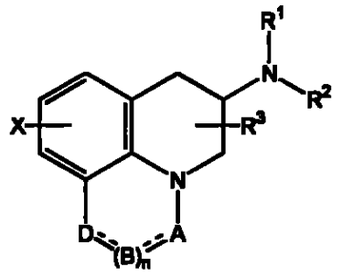
26.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque la administración del agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más al mamífero,

comprende liberar el agonista de dopamina hidrofóbico a través de una disposición de microagujas.

27.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, se libera mediante bomba de infusión, bomba piezoeléctrica, bomba electromotriz, bomba electromagnética, resorte de Belleville, iontoforesis o sonoforesis.

28.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más, tiene un logP mayor de 2.0.

29.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, es como se describe en la fórmula (I):



(I)

en donde: R^1, R^2 y R^3 son iguales o diferentes, y son H, alquilo de C_{1-6} (opcionalmente sustituido con fenilo), alquenilo o alquinilo de C_{3-5} o cicloalquilo de C_{3-10}, o en donde R^3 es como se definió anteriormente, y R^1 y R^2 son ciclizados con el átomo de nitrógeno unido para formar grupos pirrolidinilo, piperidinilo, morfolinilo, 4-metilpiperazinilo o imidazolilo; X es H, F, Cl, Br, I,

OH, alcoxi o alquilo de C_{1-6}, CN, carboxamida, carboxilo o alquilcarbonilo de C_{1-6}; A es CH, CH_2, CHF, CHCl, CHBr, CHI, $CHCH_3$, C=O, C=S, $CSCH_3$, C=NH, CNH_2, $CNHCH_3$, $CNHCOOCH_3$, CNHCN, SO_2 o N; B es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, N, NH o NCH_3; D es CH, CH_2, CHF, CHCl, CHBr, CHI, C=O, O, N, NH o NCH_3; y n es 0 ó 1, y en donde ⎯⎯ es un enlace sencillo o doble enlace, con las condiciones de que: (1) cuando n es 0 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2, entonces D es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, O, NH o N-CH_3; (2) cuando n es 0 y A es CH, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N, entonces D es CH o N; (3) cuando n es 1 y A es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, $CHCH_3$, C=O, C=S, C=NH o SO_2; y B es CH_2, CH-(halógeno), en donde halógeno es como se definió anteriormente, C=O, NH o N-CH_3, entonces D es CH_2, C=O, O, NH o N-CH_3; (4) cuando n es 1 y A es CH_2, C-SCH_3, C-NH_2, C-$NHCH_3$, C-$NHCOOCH_3$, C-NHCN o N; y B es CH o N, entonces D es CH_2, C=O, O, NH o N-CH_3; (5) cuando n es 1 y A es CH_2, $CHCH_3$, C=O, C=S, C=NH o SO_2, y B es CH o N, entonces D es CH o N; y sales farmacéuticamente aceptables del mismo.

30.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de aproximadamente 1.5 o más, se selecciona del grupo que consiste de (R)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolino-2-(1H)-tiona,

(R)-5,6-dihidro-5-(metilamino)-4H-imidazo[4,5-*ij*]-quinolin-2-(1H)-ona, y sales farmacéuticamente aceptables de los mismos.

31.- El equipo de conformidad con las reivindicaciones 3 ó 4, caracterizado además porque el agonista de dopamina hidrofóbico que tiene un logP de alrededor de 1.5 o más, está en forma de nanopartículas o nanocristales.

Industria y Comercio
SUPERINTENDENCIA

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2020
Bogotá, D.C.,

Oficio Nº 1325

Doctor:
Ramiro Castro Duque
Apoderado
Pharmacia Corporation

ASUNTO:	Radicación Nº	03 112342
	Solicitud Internacional	PCT/US2002/19918
	Fecha Inicio fase nacional	29/01/04
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento el el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).

- ☐ La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

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

El anterior requerimiento fue notificado por fijación en lista de fecha, 06 FEB. 2004.

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