Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia	**: Expediente N° 06 088181**
Asunto	**: Oposición a la solicitud de patente de Invención titulada "COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM"**
Solicitante	**: H LUNDBECK A/S**
Opositora	**:PROCAPS S.A.**

Publicada en la Gaceta de la Propiedad Industrial
N° 581 del 31 de octubre de 2007

Yo, ***ELIANA ISAURA MORENO BOHORQUEZ,*** abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad ***PROCAPS S.A.*** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada **"COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM"**, cuyo titular es **H LUNDBECK A/S,** y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 – 6 20 50 21 – Fax. (571) 6 12 19 79
E-mail: negocios@opinion-co.com - www.opinion-co.com
Bogotá Colombia

Tablet properties:

Diametrical crushing strength: 70 N

Disintegration time: 30 seconds

Friability: NA

Weight variation: 0.84% relative standard deviation (measured on 20 tablets)

Punch adhesion: None observed

Citalopram content in the composition during compression.

Tablets were sampled throughout the compression in order to measure segregation tendency. Since there is a significant size difference between the active ingredient, citalopram hydrobromide, and the inert filler, ProSolv SMCC90, as seen in table 1, it would be expected that the unequally sized components would segregate, i.e. de-mix, during transfer from blending vessel to tablet press hopper or sitting in the tablet press hopper during tabletting.

Sampling was performed 50 times at regular intervals during tabletting, corresponding to sampling at every 4000 tablets produced. Two tablets were withdrawn for each sample.

The tablets were assayed by a validated method using UV-absorption in an aqueous solution, thus analysing in total 100 tablets. The relative standard deviation in citalopram content was 1.6%

The variability in tablet strength is surprisingly low in view of the small particle size of citalopram hydrobromide as compared to the inert filler.

One possible explanation for this surprising and beneficial result may be that the tendency to segregation between small citalopram crystals and larger filler particles is uniquely balanced by the poor flow properties of the small crystals.

Example 6

Tablet prepared by direct compression of large citalopram hydrobromide crystals.

Tablet ingredients:

Citalopram, HBr	(20 % w/w)
ProSolv SMCC90	(79.5 % w/w)
Magnesium stearate	(0.5 % w/w)

Citalopram hydrobromide crystals from example 2 and ProSolv SMCC90 were blended. Magnesium stearate was added and blending continued.

Tablets (125 mg nominal weight) were produced.

The tablets had satisfactory technical properties.

Example 7

Tablet prepared by direct compression of citalopram crystals.

Tablet ingredients:

Citalopram base	(16 % w/w)
ProSolv SMCC90	(83.3 % w/w)
Magnesium stearate	(0.7 % w/w)

Citalopram base crystals from example 4 were sieved through sieve aperture of 0.3 mm and mixed with ProSolv SMCC90 for 3 minutes in a Turbula mixer. Magnesium stearate was added and blending continued for 30 seconds.

Tablets were produced on a single punch tabletting machine Korsch EK0.

Tablet properties:

Tablet strength, mg: 20

Nominel tablet weight, mg: 125

Tablet diameter, mm: 7

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

Direccion para notificaciones judiciales:
CL 80 No 78 B - 201.
De la ciudad de Barranquilla.

C E R T I F I C A

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

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a)-La fabricacion de capsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para uso y consumo humano y veterinario; b)-La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal; c)-La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas,alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados, d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos,quirurgicos,odontologicos,y hospitalarios para la salud humana y animal. e)La compra,venta,exportacion y dis-distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. f) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c). d) y e) antes descritos; g) Prestar los servicios de asesoria y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial; h)-Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista,

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

1. INTERÉS PARA ACTUAR

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

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 9 de abril de 2006, reivindicando prioridad bajo las solicitudes DK20040000382 del 2004-03-05; y, US20040550909P del 2004-03-05 y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 581 del 31 de octubre de 2007, cuya publicación internacional corresponde a la WO2005084643 del 15/09/2005.

2.2. La solicitud colombiana **06088181**objeto de la presente oposición, se refiere a partículas cristalinas de oxalato de escitalopram, caracterizadas porque la relación entre la media del tamaño de partícula y el tamaño de la partícula en el 95% del quintilo es inferior a 0,42; donde la relación entre el tamaño de partícula de la media y el tamaño de partícula en el 95% del quintilo es inferior a 0,40; donde una partícula de la media es de por lo menos 20 µm; donde el tamaño de partícula de la media de los cristales es de por lo menos 40 µm, preferiblemente está en el rango de 50-200 µm; donde la distribución del tamaño de partícula de las partículas cristalinas de oxalato de escitalopram es bimodal o polimodal y el pico

2.8.En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana **06-088181** no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

2.9.Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.9.1. **CARECE DE NOVEDAD**: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*. A la fecha de prioridad, 5 de marzo de 2004 ya era conocido, pues como se demostró, era parte del arte anterior con base en los documentos D1 y D2, una composición cristalina que contiene escitalopram, sobre el cual busca protección en el capítulo reivindicatorio.

2.9.2. **CARENCIA DE ALTURA INVENTIVA**. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."*. A la fecha de prioridad, 5 de marzo de 2004, a partir de los documentos D1 y D2 en combinación con D3 y D4, es posible deducir la conformación partículas cristalinas de oxalato de escitalopram, con una relación entre la media del tamaño de partícula y el tamaño de la partícula inferior a 0,42 o 0,40; donde una partícula de la media es de por lo menos 40 µm, preferiblemente está en el rango de 50-200 µm así como el proceso de obtención y sus dosis sólidas, sobre el cual busca protección en el capítulo reivindicatorio.

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

2.11. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **"COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM"**, cuyo titular es **H LUNDBECK A/S,** solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 581

3. PRUEBAS

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

- D1: GB2376233 publicada el 11 de diciembre de 2002.
- D2: EP1522539 publicada el 13 de abril de 2005.
- D3: WO03011278 publicada el 13 de febrero de 2003.
- D4: US4943590 publicada el 24 de julio de 1990.

6. NOTIFICACIONES

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

Señor Superintendente,

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

PROCAPS

PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA,** mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 **del C.S. de la J.**, poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. **06.088.181**, titulada **"COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM"**, cuyo titular es **H LUNDBECK A/S,** publicada en la gaceta No. 581 del 31 de Octubre de 2007.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 15 días del mes de enero de 2008.

PROCAPS S.A.
WALTER TANAKA TATEKAWA
C.C. N° 16.251.923 de Palmira
Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

DILIGENCIA DE PRESENTACIÓN
La Notaría Dieciocho del Círculo de Bogotá, D.C., hace constar que el presente documento fue presentado personalmente por
quien exhibió la C.C.
y Tarjeta Profesional
C.S.J., y declaró que la firma y la huella que aparecen en el presente documento son suyas.
BOGOTÁ D.C. 28 ENE. 2008
Victoria Bernal Trujillo
HUELLA DEL INDICE DERECHO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

RECIBO OFICIAL DE CAJA : 08 - 7,661
FECHA : ENERO 2º DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-088181- -00004-0000
Fecha: 2008-01-29 13:38:48 Dep: 2020 NUEVA CREACION
Tra: 11 PATENTE(S) Eve: 378 PRIMERA NACIONAL
Act: 400 OPOSICION OBSERVACION Folios: 71

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
LAB. PROCAPS	CONSIGNACION	BANCO DE BOGOTA	062754307	534245	29/01/2008	30,000.00
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	67772279	12/12/2007	$$$,000.00
LAB. PROCAPS	CONSIGNACION	BANCO POPULAR	050-00110-6	67772283	12/12/2007	404,000.00

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

CANT.	CENT UTIL	CONCEPTO		TOTAL CONCEPTO
1	00%	01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	246,000.00
			TOTAL : $	246,000.00

CON: DOSC CIENTOS CUARENTA Y SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

03-070[redacted]024802 PROCAPS S.A.
Barranquilla, 16 de Enero de 2008 Hr:14:57:12

No. 11692886

CAMARA DE COMERCIO DE BARRANQUILLA

********** Pag. 1
C A M A R A D E C O M E R C I O
D E B A R R A N Q U I L L A
09**********

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.
PROCAPS S.A.----------
NIT: 890.106.527-5.

VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ----------
DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO -------
CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial -----
amplio y suficiente al senor WILLIAM ALBERTO BARROS CERRA ----------
CC.No.8.715.941, y al senor ANTONIO VARELA DIAZ CC.No.72.004.699, para que en nombre y representacion de PROCAPS S.A., suscriban -----
declaraciones cambiarias, aduaneras y tributarias a que este -------
obligada la sociedad, en el giro normal de sus negocios y ----------
operaciones sociales, por tanto quedan facultados para firmarlas, como tambien los demas documentos relacionados con ellas, ----------
notificarse, aportar y solicitar las pruebas que sean necesarias.
c.-Otorgar poder especial amplio y suficiente al senor MARLON -----
TATIS PAREDES CC.No.72.176.874 y al senor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representacion de ------
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los tramites o registros de Comercio -----
Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN -----
ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----------
representacion de PROCAPS S.A.; endosen los titulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ----------
(1.000.000.000.00) M.L. CUARTO: EI representante legal de la -------
sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General -------
Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.----------

C E R T I F I C A

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

C E R T I F I C A

Que su última Renovación fue el: 20 de Marzo de 2007.

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

ANEXO 1

Carrera 13 N° 119-95, Oficina 104. Tel. (571) 2 13 12 13 ~ Fax. (571) 6 12 19 79
e-mail: negocios@oriminn-co.com ~ www.oriminn-co.com
Bogotá Colombia

(12) UK Patent Application (19) GB (11) 2 376 233 (13) A

(43) Date of A Publication 11.12.2002

(21) Application No 0219820.8

(22) Date of Filing 31.07.2001

Date Lodged 27.08.2002

(30) Priority Data
(31) 0120200 (32) 10.08.2000 (33) DK
(31) 0161400 (32) 27.10.2000

(62) Divided from Application No
0118579.2 under Section 15(4) of the Patents Act 1977

(71) Applicant(s)
H Lundbeck A/S
(Incorporated in Denmark)
Ottiliavej 7-9, DK-2500 Kobenhavn-Valby,
Denmark

(72) Inventor(s)
Per Holm
Ken Liljegren
Ole Nielsen
Swen Wagner

(51) INT CL[7]
C07D 307/88 // B01D 9/02 , C07D 307/87

(52) UK CL (Edition T)
C2C CNB CVM C1474 C213 C22Y C220 C25Y C253
C29X C29Y C31Y C311 C32Y C326 C43X C62Y C620
C650 C676 C697 C80Y C802

(56) Documents Cited
GB 2357762 A EP 1152000 A1
EP 0171943 A1

(58) Field of Search
INT CL[7] B01D 9/02, C07D 307/87
Other: Online: CAS-ONLINE, WPI, EPODOC, JAPIO,
TXTE

(74) Agent and/or Address for Service
Stevens Hewlett & Perkins
1 St Augustine's Place, BRISTOL,
BS1 4UD, United Kingdom

(54) Abstract Title
Crystals of a pharmaceutically acceptable salt of citalopram wherein the median particle size of the crystals is at least 40 microns

(57) Crystals of a pharmaceutically acceptable salt of citalopram wherein the median particle size of the crystals is at least 40 microns. Preferably, the salt is citalopram hydrochloride and more preferably, citalopram hydrobromide. Also, a method of manufacture of the salt of citalopram wherein a solution of the salt in a solvent system at a first temperature is cooled down to a second temperature then seeded by the addition of crystal of the salt of citalopram followed by a holding time at said second temperature and a controlled cooling down to a third temperature whereupon the crystals are isolated by filtration. Preferably, the solvent system comprises one or more alcohols and optionally water. More preferably, the solvent system comprises a mixture of methanol and water.

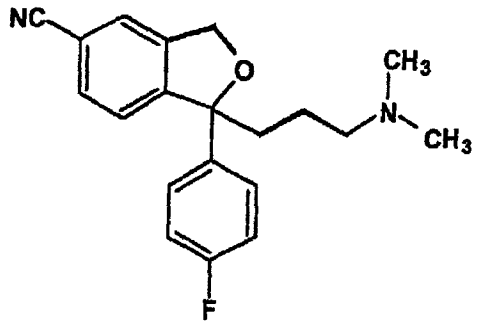
GB 2 376 233

PHARMACEUTICAL COMPOSITION CONTAINING CITALOPRAM

The present invention relates to a novel pharmaceutical composition containing citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzo-furancarbonitrile.

Background of the Invention

Citalopram is a well-known antidepressant drug that has the following structure:



It is a selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method, which may be used for preparing citalopram. The citalopram prepared was isolated in crystalline form as the oxalate, the hydrobromide and the hydrochloride salt, respectively. Furthermore, the citalopram base was obtained as an oil (B.P. 175 C/0.03 mmHg). The publication also outlines the manufacture of tablets containing salts of citalopram. Citalopram is marketed as the hydrobromide and the hydrochloride, respectively.

Manufacture of crystalline citalopram base is disclosed in co-pending DK 2000 00402. This patent publication describes the preparation of crystalline citalopram base and the use of crystalline citalopram base as an intermediate in the purification of crude citalopram hydrobromide into pure citalopram

hydrobromide. The publication also outlines the manufacture of tablets containing citalopram base.

Citalopram is marketed in a number of countries as a tablet prepared by compression of granulated citalopram hydrobromide, lactose and other excipients.

It is well recognised that preparation of tablets with a reproducible composition requires that all the dry ingredients have good flow properties. In cases, where the active ingredient has good flow properties, tablets can be prepared by direct compression of the ingredients. However, in many cases the particle size of the active substance is small, the active substance is cohesive or has poor flow properties.

Further, active substances with a small particle size mixed with excipients having a larger particle size will typically segregate or de-mix during the tabletting process.

The problem of small particle size and poor flowability, is conventionally solved by enlarging the particle size of the active substance, usually by granulation of the active ingredient either alone or in combination with a filler and/or other conventional tablet ingredients.

One such granulation method is the "wet" granulation process. Using this method, the dry solids (active ingredients, filler, binder etc.) are blended and moistened with water or another wetting agent (e.g. an alcohol) and agglomerates or granules are built up of the moistened solids. Wet massing is continued until a desired homogenous particle size has been achieved whereupon the granulated product is dried.

An alternative to the "wet" granulation method is the "melt" granulation, which is also known as the "thermal plastic" granulation process, where a low melting solid is used as the granulation agent. Initially, the dry solids are blended and heated until the binder melts. As the binder is liquefied and spreads over the surface of the particles, the particles will adhere to each other and form granules. The binder solidifies upon cooling forming a dry granular product.

Wet granulation as well as melt granulation are energy intensive unit operations requiring complicated and expensive equipment as well as technical skill.

The process used for the preparation of citalopram hydrobromide results in a product with a very small particle size around 2-20 μm that, as many other particulate products with a small particle size, has very poor flow properties. Thus, in order to achieve appropriate dosing of the citalopram during tabletting, it was considered necessary to make a granulate of citalopram with larger particle size and improved flow properties.

The citalopram tablet that is marketed is a tablet made from granulated citalopram hydrobromide with various excipients.

In view of the fact that direct compression is much simpler and cheaper than the processes involving granulation there is a desire for a process for direct compression of citalopram hydrobromide.

The obstacles that hitherto have hindered direct compression of citalopram tablets have now been circumvented after extensive laboratory research.

It has been found that larger particles, i.e. particles of a size comparable to the size of the filler, may be prepared by a new and inventive crystallisation process and that these particles are useful for the manufacture of directly compressed tablets. Accurate dosing in capsules may also be with such large particles.

It has also been found, that tablets with surprisingly small variation in the content of citalopram may be prepared by direct compression of citalopram hydrobromide having a significantly smaller particle size than the filler. Accurate dosing in capsules may also be achieved despite the small particle size of citalopram.

Objects of the Invention

It is the object of the present invention to provide a novel pharmaceutical unit dosage form containing citalopram with a suitable large particle size, wherein said unit dosage form may be prepared by direct compression.

A second object of the invention is to provide a capsule containing citalopram.

A third object of the invention is to provide large crystals of a pharmaceutically acceptable salt of citalopram suitable for use in direct compression.

A fourth object of the invention is to provide a method for manufacture of large crystals of a pharmaceutically acceptable salt of citalopram.

Summary of the Invention

The invention then, *inter alia*, comprises the following alone or in combination:

A solid unit dosage form comprising citalopram prepared by direct compression of a mixture of citalopram base or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients, or by filling of said mixture in a hard gelatine capsule.

Crystals of a pharmaceutically acceptable salt of citalopram suitable for use in a solid unit dosage form with a median particle size of at least 40 µm.

A method for the manufacture of crystals of a pharmaceutically acceptable salt of citalopram having a median particle size of at least 40 µm and suitable for use in a solid unit dosage form wherein a solution of a pharmaceutically acceptable salt of citalopram in a suitable solvent system at a first temperature is first cooled down to a second temperature then seeded by addition of crystals of said citalopram salt followed by a holding time at said second temperature and a controlled cooling down to a third temperature whereupon said crystals are isolated by conventional solid/liquid separation techniques.

The direct compression of citalopram, a filler and other pharmaceutically acceptable excipients into tablets has the great advantage, that the granulation and a drying step is avoided. Further, as the granulation step is avoided, it is no longer necessary to add a binding agent.

As used herein, "direct compression" means that the solid unit dosage form is prepared by compression of a simple mixture of the active ingredient and excipients, without the active ingredient having been subjected to an intermediate granulation process in order to embed it in a larger particle and improve its fluidity properties.

As used herein, "binder" means an agent, which is used in wet or melt granulation processes and acts as a binder in the granulated product.

As used herein, "particle size distribution" means the distribution of equivalent spherical diameters as determined by laser diffraction at 1 bar dispersive pressure in a Sympatec Helos equipment. "Median particle size", correspondingly, means the median of said particle size distribution.

As used herein, "refluxing temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

Thus in one embodiment of the invention, the present invention relates to a tablet prepared by direct compression of a mixture of citalopram base or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients.

In another embodiment, the present invention relates to a capsule prepared by filling a mixture of citalopram base or a pharmaceutically acceptable salt thereof and pharmaceutically acceptable excipients in a hard gelatine capsule.

In one embodiment, the present invention relates to a solid unit dosage form comprising citalopram in crystals with a median particle size below 20 µm.

In another embodiment, the present invention relates to a solid unit dosage form comprising citalopram in crystals with a median particle size of at least 40 µm, preferably in the range of 40 – 200 µm, even more preferred 45 – 150 µm and most preferred 50 – 100 µm.

Flow, segregation and demixing properties and, hence, the suitability of the citalopram crystals for direct compression depend, besides the median particle size, on the particle side distribution.

Preferably, the solid unit dosage forms according to the invention do not contain a binder.

The solid unit dosage form according to the invention may contain 2-60 % w/w active ingredient calculated as citalopram base, preferably 10-40 % w/w active ingredient calculated as citalopram base, and more preferred 15-25 % w/w active ingredient calculated as citalopram base. Suitably, the solid unit dosage form of the invention contains 20 % w/w active ingredient calculated as citalopram base.

In particular, the present invention relates to a solid unit dosage form wherein the active ingredient is citalopram hydrobromide, or citalopram hydrochloride. Preferably the active ingredient contained in the solid unit dosage form of the invention is citalopram hydrobromide.

The solid unit dosage form according to the invention may contain a filler selected from lactose, or other sugars e.g. sorbitol, mannitol, dextrose and sucrose, calcium phosphates (dibasic, tribasic, hydrous and anhydrous), starch, modified starches, microcrystalline cellulose, calcium sulphate and/or calcium carbonate. In a preferred embodiment, the solid unit dosage form of the invention does not contain lactose.

Suitably the filler is a microcrystalline cellulose such as ProSolv SMCC90 manufactured by Penwest Pharmaceuticals or Avicel PH 200 manufactured by FMC Corporation.

Besides the active ingredient and filler, the solid pharmaceutical unit dosage forms may include various other conventional excipients such as disintegrants, and optionally minor amounts of lubricants, colorants, and sweeteners.

Lubricants used according to the invention may suitably be one or more of the following metallic stearates (magnesium, calcium, sodium), stearic acid, wax, hydrogenated vegetable oil, talc and colloidal silica.

Suitably the lubricant is magnesium stearate or calcium stearate

Disintegrants include sodium starch glycolate, croscarmellose, crospovidone, low substituted hydroxypropylcellulose, modified cornstarch, pregelatizined starch and natural starch.

The solid, pharmaceutical unit dosage form of the invention may be prepared by conventional methods using a tablet press with forced feed capability.

The filled, hard gelatine capsule of the invention may be prepared by conventional methods using a capsule filler suitable for powder filling.

In one embodiment of the present invention the crystals of a pharmaceutically acceptable salt of citalopram have a median particle size in the range of 40 - 200 µm, preferably 45 – 150 µm and even more preferred 50 – 120 µm.

In a preferred embodiment of the present invention the crystals are of citalopram hydrobromide or citalopram hydrochloride, preferably citalopram hydrobromide.

In yet another embodiment of the present invention crystals of a pharmaceutically acceptable salt of citalopram having a median particle size of at least 40 µm and suitable for use in a solid unit dosage form are crystallised from a solution of a pharmaceutically acceptable salt of citalopram in a suitable solvent system. Said solvent system may comprise one or more alcohols and optionally water, preferably the solvent system is a mixture of methanol and water, wherein the methanol:water weight ratio preferably is in the range of 5:1 to 50:1; even more preferred 10:1 to 30:1 and most preferred 15:1 to 25:1. Said pharmaceutically acceptable salt of citalopram is preferably dissolved in the solvent system at a temperature in the range between 50 °C and the refluxing temperature of the solvent system, preferably between 60 °C and the refluxing temperature and more preferred between 64 °C and the refluxing temperature. The amounts of pharmaceutically acceptable salt of citalopram and solvent used are preferably corresponding to a solvent:solute weight ratio in the range of 0.5:1 to 5:1, more preferred 0.7:1 to 2:1 and most preferred 0.9:1 to 1.5:1. The solution of a pharmaceutically acceptable salt of citalopram is cooled down to a temperature, the seeding temperature, in the range of 20-40 °C, preferably 25-35 °C, whereupon it is seeded with citalopram crystals and kept at said seeding temperature for a holding time for crystal growth in the range of 30 minutes to 7 days, preferably 1 hour to 4

days and more preferred 12 to 36 hours. After said holding time, the crystallisation batch is gradually cooled down in a controlled way from the seeding temperature to the temperature at which the crystals will be isolated from the mother liquor wherein said gradual cooling down is done over a time span in the range of 5 minutes to 6 hours, preferably 15 minutes to 4 hours and more preferred 30 minutes to 2 hours. The crystals of said pharmaceutically acceptable salt of citalopram are preferably isolated from the mother liquor at a temperature in the range of 0-20 °C, more preferred 5-15 °C, using conventional separation techniques, e.g. filtration.

The small crystals of a pharmaceutically acceptable salt of citalopram used in one embodiment of the invention may be produced according to methods described in US 4,136,193.

The crystals of citalopram base used in one embodiment of the invention may be produced according to methods described in NL patent No. 1016435.

In the following, the invention is illustrated by way of examples. However, the examples are merely intended to illustrate the invention and should not be construed as limiting.

Example 1

Crystallisation of citalopram hydrobromide into large crystals

Citalopram hydrobromide (200 g) is dissolved in a mixture of methanol (200 g) and water (20 g) at 69 °C. The solution is cooled down to 30 °C, seeded with citalopram hydrobromide crystals and kept at 30 °C for 24 hours, whereupon it is cooled down to 10 °C within 1 hour. The crystals are isolated by filtration, washed with cold methanol and dried. The particle size distribution for the resulting crystals is listed in table 1.

Example 2

Crystallisation of citalopram hydrobromide into large crystals

Citalopram hydrobromide (12.0 kg) is dissolved in a mixture of methanol (12.5 kg) and water (1.2 kg) at reflux. The solution is cooled down to 30 °C, seeded with citalopram hydrobromide crystals (27 g) and kept at 30 °C for 16

hours, whereupon it is cooled down to 10 °C within 1 hour. The crystals are isolated by filtration, washed with cold (10 °C) methanol (3.5 kg) and dried. The particle size distribution for the resulting crystals is listed in table 1.

Example 3

Crystallisation of citalopram hydrobromide into small crystals

Citalopram hydrobromide (200 kg) is dissolved in a mixture of methanol (170 L) and acetone (680 L) at 56 °C. The solution is cooled down to 15 °C, seeded with citalopram hydrobromide crystals (50 g), hexane (1600 L) is gradually added within 60 minutes, whereupon the suspension is left standing with moderate stirring and cooling for 8 hours. The crystals are isolated by filtration, washed first with a cold (10 °C) mixture of acetone (50 L) and hexane then with cold (10 °C) hexane (220 L) and dried. The particle size distribution for the resulting crystals is listed in table 1.

Example 4

Crystallisation of citalopram as the free base.

Citalopram hydrobromide (101 g) is suspended in water (500 mL) and toluene (500 mL). NaOH (60 mL, 5 N (aq)) is added and the mixture (pH>10) is stirred for 15 min before the phases are separated. The organic phase is washed with water (2 x100 mL) and filtered through a pad of filter help. The volatiles are removed *in vacuo* and the title compound is obtained as an oil. n-Heptane (400 mL) is added and the mixture is heated to 70 °C. On cooling, crystals forms. The white crystals of citalopram base are filtered off and dried at ambient temperature over night *in vacuo*.

Table 1: Particle size distribution (Sympatec Helos) for citalopram hydrobromide crystals and ProSolv SCMC90

Quantile (%)	Example 1 (µm)	Example 2 (µm)	Example 3 (µm)	ProSolv SCMC90 (µm)
95	465.43	549.42	96.96	279.94
90	342.89	352.23	72.27	231.66
50	96.87	52.70	14.04	114.17
10	16.54	11.97	1.19	32.10
5	8.23	6.67	0.82	20.56

Example 5

Tablet prepared by direct compression of small citalopram hydrobromide crystals.

Tablet ingredients:		
Citalopram, HBr	5800 g	(20 % w/w)
ProSolv SMCC90	23055 g	(79.5 % w/w)
Magnesium stearate	145 g	(0.5 % w/w)

Citalopram hydrobromide crystals from example 3 and ProSolv SMCC90 were blended at 7 rpm for 10 min in a 100 litre Bohle PTM 200 mixer. Magnesium stearate was added and blending continued for 3 min.

25 kg of the resulting mixture was tabletted (125.000 tablets/hour) on a 30 station Fette P 1200/IC tablet press fitted with oblong, embossed, scored 5,5 x 8 mm punches. Tablet core weight was set to 125 mg. The nominal yield was 200.000 tablets. The tablet press was run until the mixture level was just above the forced feeder, i.e. the tabletting was continued as long as possible in order to identify possible segregation tendencies in the last quantities of mixture.

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Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.T):

Int Cl (Ed.7): B01D 9/02, C07D 307/87

Other: Online: CAS-ONLINE, WPI, EPODOC, JAPIO, TXTE

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
A, P	GB 2357762 A	(H. LUNDBECK A/S) see example 1.	
A, E	EP 1152000 A1	(SUMIKA FINE CHEMICALS COMPANY LTD) see example 4, figure 9.	
X	EP 0171943 A1	(H. LUNDBECK A/S) see example 2.	1-32

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and or state of the art.
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