Industria y Comercio
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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FORMULARIO UNICO DE OPOSICION
2000-12

1 OPOSICION A:

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

2 SOLICITUD PUBLICADA

Número del expediente: 06 088.181
Solicitante: H. LUNDBECK A/S
Apoderado: EMILIO FERRERO
Título de la nueva creación o denominación del signo:
"COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM."
Gaceta: 581 de 31 de Julio 2007, Número de Publicación 665

3 OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: **(1)Tecnoquímicas S.A.** **(2) Lafrancol S.A.** Dirección: **(1) Calle 23 No. 7-39** **(2) Diag. 107 No. 36-45** Teléfono: **(1) (092) 882.55.55** **(2) 622.04.66** Fax: **(1) (092) 883.88.59** **(2) 236.55.34** Domicilio: **(1) Cali (2) Bogotá, D.C.**	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Número: **(1) 890 300 466-5** **(2) 890 301 463 -8**
REPRESENTANTE O APODERADO (74)	Nombre: **José Luis Reyes Villamizar** Dirección: **Cra. 17 No. 88-23, Of. 205** Teléfono: **621.26.31** E-mail: **reyes_abogados@etb.net.co** Fax: **621.25.42** Domicilio: **Bogotá, D.C.**	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: **79'152.473 de Usaquén** **TP 44655**

4 FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser suceptibles de aplicación industrial), 16 (una invención se considera nueva cuando no es obvia, ni se deriva de manera evidente del estado de la técnica) y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia)

Justificación: Ver anexo

168

5 **Comprobante de pago No.** ① 08-6,799 (Oposición) **Fecha** ENERO 25 DE 2008
② 08-8,077 ENERO 30 DE 2008
_____ (Prórroga) Fecha _____

6 **Anexos:**

- ☐ Comprobante de pago de la tasa
- ☐ Poderes, si fuere el caso
- ☐ Pruebas de los fundamentos de la oposición
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☐ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☐ Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: _____

REYES & REYES
A B O G A D O S

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 06-088-181**

TÍTULO SOLICITADO: **"COMPOSICIÓN CRISTALINA QUE CONTIENE ESCITALOPRAM."**

PUBLICACIÓN: **Gaceta 581 de 31 de Octubre de 2007, Nº de publicación 665.**

PRIORIDAD: **DK PA200400382 del 05/03/2004**

SOLICITANTE: **H. LUNDBECK A/S.**

APODERADO: **EMILIO FERRERO**

TRÁMITE: **Presentación de Oposición**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de las sociedades **TECNOQUÍMICAS S.A., y LAFRANCOL S.A.,** en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente 06 088.181, por no cumplir con lo dispuesto por los artículos 14, 16 y 18 de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS S.A.**, y a **LAFRANCOL S.A.,** legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría injustificadamente el empleo de ciertas sustancias, derivados y procesos que a nuestro juicio carecen de nivel inventivo, en detrimento de sus legítimos intereses comerciales. De igual manera mis clientes están interesados, por su misma condición de industrias farmacéuticas, en evitar la concesión de privilegios de patente que incumplan los requisitos materiales de patentabilidad establecidos en las normas vigentes, y que supongan un riesgo para la libre competencia.

III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud Colombiana en trámite que se refiere a partículas cristalinas de oxalato de escitalopram, método de obtención que comprende el cierre del anillo de R-4-[4 -dimetilamino) -1-(4'-fluorofenil)-hidroxibutil] -3- (hidroximetil) -benzonitrilo bajo condiciones acidas; la reducción de impurezas en dicho escitalopram, citalopram o mezcla no racémica de R y S citalopram con el tratamiento de un depurador de grupos hidroxilo (anhídridos) y el enfriamiento gradual y controlado de dicha solución de oxalato de escitalopram en un sistema solvente y la siembra o adición de cristales de oxalato de escitalopram a la misma; así como la forma de dosificacion sólida (tableta recubierta o cápsula de gelatina dura) obtenida mediante compresión directa, incumple los requisitos de patentabilidad indispensables para otorgársele el privilegio de patente de invención, tal y como se demuestra a través de los siguientes argumentos:

3.1. LA SAL DE OXALATO DE ESCITALOPRAM, CARECE DE NOVEDAD Y NIVEL INVENTIVO.

El principio activo conocido por el nombre genérico de ESCITALOPRAM, **incluyendo en general sus sales,** entre ellas la sal cristalina de Bromhidrato de Escitalopram, ciertos procesos de obtención y de cristalización, al igual que su utilidad y empleo como antidepresivo, han sido revelados al menos desde la publicación de la patente americana US 4,650,884 en **17-03-1987**, esto es, hace veinte (20) años. Además, la simple lectura de la reivindicación 3 de la citada

dimethylaminopropyl) -1- (4´-fluorophenyl)-1, 3- dihydroisobenzofuran -5-Carbonitrile (ESCITALOPRAM), sino, como se ha dicho, **sus sales ácidas de adición farmacéuticamente aceptables**.

La generalidad de esta reivindicación permite concluir que **la sal oxalato** que ahora se pretende, en tanto **es una sal ácida de adición farmacéuticamente aceptable, ya había sido revelada** en el documento reseñado, razón por la cual su conocimiento afecta sin lugar a dudas la **novedad** de la solicitud en curso.

Otro documento que revela la sustancia en mezcla racémica o Citalopram es la patente DE 2657013 equivalente a la US 4136193 presentada el 7 de junio de 1977 y publicada el **23 de enero de 1979**, de título "Anti-depressive substituted 1-Dimethylaminopropyl-1-Phenyl Phthalans", en la cual se revelan compuestos seleccionados del grupo que consiste de phthalanos de fórmula (I), entre los que se encuentra 1-[4´-fluorophenyl] -1-[3-[Dimethyl-amino] propyl]- -5-phthalan carbonitrile (Citalopram) o una sal de adición ácida del mismo farmacéuticamente aceptable. Más específicamente se describe que el **Citalopram preparado fue aislado en forma cristalina como sal Oxalato**, Bromhidrato y Clorhidrato; y también se revelan composiciones farmacéuticas en forma de tabletas para el tratamiento de la depresión.

Del mismo modo, la patente US 4,943,590, publicada el **24/07/1990**, es decir, catorce (14) años antes de la fecha de prioridad de esta solicitud, y titulada "Pharmaceutically useful (+)- 1-(3-(dimethylaminopropyl) -1-(4´-fluorophenyl) -1,3-dihydrobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof" revela sales farmacéuticamente aceptables de los enantiómeros de Citalopram formadas con ácidos orgánicos o inorgánicos no tóxicos. También dice:

Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether, ethyl acetate or dicloromethane, with the desired salt separating directly. Exemplary of such organic salt are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, oxalic, salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acid, as well as the 8-halotheophyllines, for example 8-bromotheophylline.

Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

Como vemos, la posibilidad de formar "fácilmente, por métodos conocidos en el estado del arte", la sal de Oxalato de Citalopram mediante la reacción de Citalopram con el ácido Oxálico está expuesta en forma expresa en este documento, razón por la cual, la sal revelada en la solicitud que nos ocupa carece por completo, una vez más, del requisito de **Novedad.**

Pese a lo anterior, si en gracia de discusión se estuviera frente a una ausencia de revelación textual de la sal cristalina que específicamente se reivindica, y si esta circunstancia formal permitiera hablar de Novedad en el sentido material de la palabra, es necesario determinar si la eventual y pretendida ausencia de revelaciones explícitas y textuales transmite a la solicitud el indispensable requisito de **Nivel Inventivo**.

3.2. LAS PARTÍCULAS CRISTALINAS DE OXALATO DE ESCITALOPRAM, CARECEN DE NOVEDAD Y NIVEL INVENTIVO.

Ahora bien, frente al hecho de que el oxalato de Citalopram se encuentre en partículas cristalinas, me permito llamar la atención de este Despacho para demostrar que tales **partículas cristalinas** también pertenecen al estado del arte puesto que la anterioridad US 4,943,590 en el ejemplo 2 en donde se hace la

- **La sal del ácido oxálico** del isómero (+)-1-(3-(dimethylaminopropyl)-1-(4´-fluorophenyl) -1,3-dihydrobenzofuran-5-carbonitrile **cristaliza** desde acetona, obteniéndose una sal con MP: 147°-148°C, [α]D= +12.31° (c=1, CH_3OH);

- **La sal del ácido oxálico** del isómero (-)-1-(3-(dimethylaminopropyl)-1-(4´-fluorophenyl) -1,3-dihydrobenzofuran-5-carbonitrile **cristaliza** desde acetona, obteniéndose una sal con MP: 147°-148°C, [α]D= +12.08° (c=1, CH_3OH).

3.3. LAS PARTÍCULAS CRISTALINAS DE ESCITALOPRAM PARA COMPRESIÓN DIRECTA, CARECE DE NOVEDAD Y NIVEL INVENTIVO.

Si ahora analizamos que el fundamento de invención de la solicitud en trámite estuviera dado por los tamaños de partículas proporcionados y la posibilidad de usar tales cristales con esos tamaños en compresión directa –tal como se afirma en la parte descriptiva de la solicitud colombiana en trámite-, me permito decir que, la patente US 4,943,590 tantas veces mencionada, si bien no se refiere de manera textual a la forma de obtener tabletas de este principio activo mediante compresión directa, si revela la posibilidad de preparar tabletas donde el principio activo es principalmente mezclado con adyuvantes ordinarios de tabletas tales como almidón de maíz, almidón de papa, talco, Estearato de magnesio, gelatina, lactosa, gomas, entre otros.

Como puede verse, desde 1990 era conocida la posibilidad de fabricar tabletas donde el principio activo corresponde a (+) Citalopram en la forma de una sal ácida de adición (entre las que puede encontrarse Oxalato de Citalopram), viables y aptas para el consumo humano, como quiera que entre los objetivos de la anterioridad mencionada está en obtener un producto final sea cual fuere el proceso para llegar a el, que satisfaga al humano luego de la administración del mismo.

Para continuar con este punto de discusión y si estuviéramos frente a la supuesta novedad o nivel inventivo de someter a Citalopram o a una de sus sales a

publicación británica GB 2 357 762 A publicada el **04/07/2001**, es decir, antes de la fecha de prioridad de esta solicitud, en la cual se revela que:

> In yet another aspect, a pharmaceutical formulation of the free base of citalopram, or a hydrobromide or hydrochloride prepared from said base, is provided. Preferably the formulation is for oral administration.
>
> The formulations according to the invention may be prepared by direct compression of citalopram in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of citalopram, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

Es claro que en el estado del arte ya se sugería que formulaciones de Citalopram pudieran ser preparadas por compresión directa, por lo que puede pensarse que para esta fecha y para el solicitante H- Lundbeck A/S ya se había encontrado que "*este proceso es mucho más simple y económico que aquellos procesos que involucran granulación*", (tal como lo afirma el solicitante en la parte descriptiva de la solicitud colombiana), por lo que el problema técnico planteado ya se había resuelto en **julio 4 de 2001**.

Ahora bien, si una persona medianamente versada en la materia, conociendo la sustancia en cuestión desde hace más de 20 años, y deduciendo en consecuencia las eventuales dificultades en materia de formulación y en especial de compresión debido entre otras razones al tamaño de partícula, necesariamente iniciaría actividades experimentales orientadas a solucionar los problemas en cuestión.

3.4. LA CARACTERIZACIÓN EN FUNCIÓN DE LOS TAMAÑOS DE PARTÍCULAS CARECE DE NIVEL INVENTIVO

Si en gracia de discusión no estuviese descrito de manera textual en el arte anterior el tamaño de partícula revelado en la solicitud colombiana en trámite para la sustancia Oxalato de Escitalopram, me permito llamar la atención del Despacho a la muy conocida posibilidad de modificar la solubilidad, disolución y biodisponibilidad de principios activos manipulando el tamaño de partícula de los mismos (o su área o su distribución de tamaño). Lo anterior es tan evidente que se ha convertido en una rutina requerida en lineamientos de la FDA cuando se está

partícula de un polvo es crucial en el desarrollo galénico de formulaciones farmacéuticas, tanto en su empleo en la fabricación de cápsulas, comprimidos, y suspensiones, entre otras formas farmacéuticas; así mismo, el tamaño de partícula de los cristales influye en la capacidad de compresión, y su uniformidad puede evitar problemas de segregación.

3.5. EL MÉTODO DE MANUFACTURA DE LAS PARTÍCULAS CRISTALINAS DE OXALATO DE ESCITALOPRAM CARECE DE NIVEL INVENTIVO.

En este punto me quiero referir a que el método planteado para la manufactura de las partículas cristalinas de Oxalato de Escitalopram el cual comprende (reivindicaciones 26 a 35) en una de sus etapas, un enfriamiento gradual de la solución que contiene dicho principio activo en un sistema solvente adecuado (alcohol y opcionalmente agua, o preferiblemente etanol), carece de nivel inventivo puesto que, es ampliamente conocido que para efectuar la cristalización de un sólido hay que partir de una Solución Sobre-Saturada, la cual se puede obtener por enfriamiento de la solución o por la eliminación de una parte del Disolvente (por ejemplo: por evaporación) a fin de aumentar la concentración del soluto, otra forma consiste en añadir un tercer componente que tenga una mayor solubilidad que el componente que se desea cristalizar.

Luego de esto, la rapidez del enfriamiento juega un papel importante puesto que ella definirá el tamaño de los cristales resultantes, un enfriamiento rápido producirá cristales pequeños, mientras que un enfriamiento lento producirá cristales grandes; es por esto que el método de la solicitud colombiana hace un **enfriamiento gradual** de la solución que contiene Oxalato de Escitalopram donde se espera que se genere un cristal más grande que pueda tener mejores propiedades de flujo.

También es importante recordar que el crecimiento cristalino se inicia cuando un cristal diminuto que se haya formado extrae de su entorno más material de su misma constitución; a veces, en ausencia de este primer cristal, o semilla, la cristalización no se produce, y la solución queda supersaturada. Por lo tanto, y en algunas ocasiones es necesario adicionar un cristal de dicha sustancia o núcleo de crecimiento en la etapa enfriamiento para que puedan ser generados los cristales de interés, en consecuencia, el método propuesto en la solicitud

colombiana en trámite (reivindicaciones 28 a 37) no cumple con el requisito de nivel inventivo puesto que la etapa de adición de un cristal con el fin de producir la nucleación y formación de los cristales finales es ampliamente reconocido en el estado del arte.

Ahora bien, y por si fueran pocos los argumentos proporcionados hasta el momento, es necesario citar dos anterioridades más que sin lugar a duda afectan los requisitos de patentabilidad necesarios para ostentar la concesión de la misma, debido a que muestra más detalladamente y en conjunto, muchos de los parámetros consignados en la solicitud colombiana en trámite, veamos:

A. La publicación internacional PCT/WO/03/000672 del 3 de Enero de 2003 y titulada "PROCESS FOR THE PREPARATION OF RACEMIC CITALOPRAM AND/OR S-CITALOPRAM BY SEPARATION OF A MIXTURE OF R- AND S-CITALOPRAM" revela:

> The invention relates to a process for the preparation of racemic citalopram and/or S- or R-citalopram by separation of a mixture of R- and S-citalopram with more than 50 % of one of the enantiomers into; a fraction of racemic citalopram and/or a fraction of S-citalopram or R-citalopram containing low amounts of the other enantiomer. The invention also relates to a process for the preparation of racemic as well as enantiomerically pure citalopram from the compound R-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile.
>
> (...)
>
> Alternatively, if the mother liquor obtained from the precipitation is acidic, S-citalopram (or R-citalopram) may be isolated from the mother liquor by basifying the mother liquor, followed by phase separation, or extraction with a solvent and evaporation of the solvent, and thereafter optionally conversion of S-citalopram (or R-citalopram) into an acid addition salt thereof, preferably the oxalate salt.
>
> (...)

In still a further embodiment of the invention, the mixture of R- and S-citalopram with more than 50 % of the R-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the S-enantiomer by ring closure in presence of an acid.

(...)

Suitable solvents for the precipitation and recrystallisation of citalopram salts are protic solvents such as water, alcohols such as methanol and ethanol, ketones such as acetone, and mixtures thereof or aprotic solvent such as acetonitrile or diglyme.

(...)

Example 4

Preparation of S-citalopram oxalate from R-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (R/S ratio: 95,7/4,3).

Acidic ring closure:

R-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (67.5 g, R/S ratio: 95,7/4,3) was dissolved in toluene (315 mL). At room temperature, a mixture of sulphuric acid (26 g, 96%) and ice (10 g) was added. The mixture was stirred at 78-85 °C for 2 hours. The reaction mixture was cooled and 40 mL water was added. Aqueous ammonia (25% by weight) was added to give a pH 9.5-10.0. The mixture was heated to 55 °C (10 minutes). The phases were separated and the toluene phase was washed three times with water (3 x 65 mL). The toluene was removed at reduced pressure at a maximum of 60 °C to give an oil (oil A). Yield: 63 g (99%).

(...)

Además reivindica:

9. The process according to claims 1-2 or 4-7 **characterised in that** the mother liquor is acidic and S-citalopram is isolated from the mother liquor by basifying the mother liquor, followed by phase separation or extraction with a solvent and evaporation of the solvent, and thereafter optionally conversion of S-citalopram into an acid addition salt thereof, preferably the oxalate salt.

14. The process according to claims 1-6 and 8-9 **characterised in that** mixture of R- and S-citalopram with more than 50 % of the R-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the S-enantiomer by ring closure in presence of an acid.

18. The process according to claims 13-16 **characterised in that** the acid used in the ring-closure reaction is a mineral acid, a carboxylic acid, a sulfonic acid or sulfonic acid derivative.

Este documento enseña claramente que la obtención de oxalato de escitalopram, y más específicamente, la obtención de R y S-citalopram se hace a través del cierre del anillo de la mezcla de R y S-4-[4-dimetilamino)-1-(4'-fluorofenil)-hidroxi-butil]-3-(hidroximetil)-benzonitrilo bajo condiciones ácidas, y más específicamente, **el ejemplo 4 revela que escitalopram Oxalato se puede obtener a partir de R-4-[4-dimetilamino)-1-(4'-fluorofenil)-hidroxibutil]-3-(hidroximetil)-benzonitrilo mediante el cierre del anillo en presencia de ácido sulfúrico;** así mismo, la anterioridad nos deja ver que el S-citalopram es aislado del licor madre por un determinado método, lo que en consecuencia permite desvirtuar el nivel inventivo de la solicitud colombiana en trámite, específicamente en lo referente a sus reivindicaciones 37, 38 y 46.

B. Por su parte, la solicitud internacional WO 03/011278 publicada el 13 de Febrero de 2003 y titulada "CRYSTALLINE COMPOSITION CONTAINING ESCITALOPRAM" revela en la parte descriptiva:

- La preparación cristalina de la sal de oxalato de Escitalopram
- Proporciona partículas cristalinas de escitalopram apropiadas para uso en compresión directa
- Un método para la manufactura de partículas cristalinas de Oxalato de Escitalopram
- Una forma de dosificación unitaria que contiene partículas cristalinas de Oxalato de Escitalopram, donde dicha forma de dosificación puede ser una tableta, la cual preferiblemente puede ser preparada por compresión directa, o

En cuanto al método de manufactura describe:

A method for the manufacture of crystalline particles of escitalopram oxalate having a median particle size of at least 40 µm and suitable for use in a solid unit dosage form wherein said method comprises that a solution of escitalopram oxalate in a suitable solvent system at a first temperature is gradually cooled down to a second temperature maintaining a controlled cooling profile and seeding the crystallisation batch by addition of crystals of escitalopram oxalate at least once during the cooling and followed by a holding time at said second temperature whereupon said crystals are isolated by conventional solid/liquid separation techniques.

En cuanto a la forma de dosis unitaria describe:

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

The solid unit dosage form according to the invention may contain 1-60% w/w active ingredient calculated as escitalopram base, preferably 4-40% w/w active ingredient calculated as escitalopram base, and more preferred 6-10% w/w active ingredient calculated as escitalopram base. Suitably, the solid unit dosage form of the invention contains 8% w/w active ingredient calculated as escitalopram base.

Preferably the lubricant is one or more selected from the group comprising talc, magnesium stearate or calcium stearate. Suitably the lubricant is a combination of talc and magnesium stearate. The weight percent of magnesium stearate in the solid unit dosage form is preferably in the range of 0.4% to 2%, and more preferred in the range of 0.7% to 1.4%.

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

Tablet core		
Escitalopram oxalate	2554 g	(10.2 % w/w)
Talc	1400 g	(5.6 % w/w)
ProSolv SMCC90	19896 g	(79.6 % w/w)
Ac-Di-Sol	900 g	(3.6 %
Magnesium stearate	250 g	(1.0 % w/w)

Film coating		
Opadry OY-S-28849, white	625 g	(2.5 % w/w of core weight)

En cuanto a las partículas cristalinas de Oxalato de Escitalopram, sus tamaños y métodos de obtención, revela:

Thus in one embodiment of the present invention the crystalline particles of escitalopram oxalate have a median particle size of at least 40 µm, preferably in the range of 50 – 200 µm.

In another embodiment of the present invention crystalline particles of escitalopram oxalate having a median particle size of at least 40 µm, preferably in the range of 50 – 200 µm, and suitable for use in a solid unit dosage form are crystallised from a solution of escitalopram oxalate in a suitable solvent system. Said solvent system may comprise one or more alcohols and optionally water, preferably the solvent system is ethanol. Escitalopram oxalate 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 70 °C and the refluxing temperature, suitably the escitalopram oxalate is dissolved at the refluxing temperature. The amounts of pharmaceutically acceptable salt of escitalopram and solvent used are preferably corresponding to a solvent:solute weight ratio in the range of 0.05:1 to 0.6:1, more preferred 0.1:1 to 0.5:1 and most preferred 0.2:1 to 0.4:1. The solution of escitalopram oxalate is gradually cooled down to the temperature, at which the crystals will be isolated from the mother liquor, in the range of 0-20 °C, preferably 0-15 °C, and more preferred 7-15 °C maintaining a controlled cooling profile so that the cooling rate in an initial cooling period does not exceed 0.6 °C/min, and preferably the cooling rate is kept within the range of 0.2 – 0.4 °C/min, and said initial cooling period extends until the temperature of the crystallisation batch is below 60 °C, preferably below 50 °C and more preferred below 40 °C, suitably the cooling rate may be kept in this range for the entire cooling. The crystallisation batch is seeded by addition of crystals of escitalopram oxalate at least once during the cooling time in order to avoid excessive supersaturation with respect to escitalopram oxalate and resulting spontaneous crystallisation into small crystalline particles. The seeding is preferably repeated in order to ensure constant presence of crystalline escitalopram oxalate during the cooling, suitably the crystallisation batch is seeded semicontinuosly until crystallisation has started. The crystallisation batch is kept at said second temperature for a holding time for crystal growth for at least 1 hour, preferably in the range of 4 to 24 hours and more preferred 6 to 12 hours. After said holding time, the crystalline particles of escitalopram are isolated from the mother liquor using conventional separation techniques, e.g. filtration.

Adicionalmente, en el capítulo reivindicatorio se consigna:

1. Crystalline particles of escitalopram oxalate, **characterised in that** the median particle size of the crystals is at least 40 µm.

2. Crystalline particles according to claim 1, **characterised in that** the median particle size of the crystals is in the range of 50-200 µm.

3. Method for manufacture of crystalline particles of escitalopram oxalate according to any of claims 1-2, **characterised in that** the method comprises gradual cooling of a solution of escitalopram oxalate in a suitable solvent system from a first temperature to a second temperature while maintaining a controlled cooling profile and seeding said solution of escitalopram oxalate by addition of crystals of escitalopram oxalate during said cooling followed by a holding time at said second temperature.

5. The method according to any of claims 3-4, **characterised in that** the solvent system comprises one or more alcohols and optionally water.

6. The method according to claim 5, **characterised in that** the solvent system is ethanol.

7. The method according to any of claims 3-6, **characterised in that** the solute:solvent weight ratio is in the range of 0.05:1 to 0.6:1, preferably 0.1:1 to 0.5:1 and more preferred 0.2:1 to 0.4:1.

8. The method according to any of claims 3-7, **characterised in that** said first temperature is 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 70 °C and the refluxing temperature.

9. The method according to any of claims 3-8, **characterised in that** said second temperature is in the range of 0-20 °C, preferably 0-15 °C and more preferred 7-15 °C.

12. The method according to any of claims 10-11, **characterised in that** said cooling rate is kept within the range of 0 – 0.6 °C/min, preferably in the range of 0.2 –0.4 °C/min.

13. The method according to any of claims 3-12, **characterised in that** said seeding is done two or more times during the initial cooling.

17. The solid unit dosage form according to claim 16, **characterised in that** it is a tablet prepared by direct compression of a mixture of escitalopram oxalate and pharmaceutically acceptable excipients.

18. The solid unit dosage form according to claim 17, **characterised in that** it the tablet is coated.

19. The solid unit dosage form according to claim 16, **characterised in that** it is prepared by filling a mixture of escitalopram oxalate and pharmaceutically acceptable excipients in a hard gelatine capsule.

20. The solid unit dosage form according to any of claims 16-19, **characterised in that** it does not contain a binder.

22. The solid unit dosage form according to any of claims 16-21, **characterised in that** it contains a filler selected from lactose, sugars, preferably sorbitol, mannitol, dextrose, and/or sucrose, calcium phosphates, preferably dibasic, tribasic, hydrous and/or anhydrous, starch, modified starches, microcrystalline cellulose, calcium sulfate and/or calcium carbonate.

28. The solid unit dosage form according to any of claims 16-27, **characterised in that** it is substantially free of lactose.

Como se observa, este documento revela absolutamente todas las características relacionadas con los cristales obtenidos de oxalato de escitalopram (tamaño, distribución de tamaño) que se describe en la solicitud colombiana en trámite; así mismo, los detalles del proceso de obtención de dichos cristales, las condiciones de cristalización, específicamente lo relacionado a solventes, rangos de temperatura y proporciones entre soluto y solvente; y por si fuera poco, también menciona absolutamente todas las características de las formulaciones sólidas (tabletas por compresión directa y recubiertas o cápsulas de gelatina dura) específicamente en lo que tiene que ver con las cantidades y tipos de excipientes presentes en dichas formulaciones.

Con esto queda indiscutiblemente desvirtuada la novedad y/o el nivel inventivo de lo reivindicado en la solicitud colombiana en trámite, especialmente, de las reivindicaciones 4, 5, 7, 10 y 12 a 25 y 28 a 37, considerando que:

* Las reivindicaciones 4, 5, 7 y 10 de la solicitud en trámite revelan que las

medio de por lo menos 40μm, preferiblemente está en el rango de 50-200μm, idéntico al revelado en las reivindicaciones 1 y 2 de la anterioridad WO 03/011278

* La forma de dosificación unitaria de las reivindicaciones 12 a 25 de la solicitud en trámite es idéntica a la revelada en las reivindicaciones 16 a 28 de la anterioridad WO 03/011278

* El método de manufactura de las partículas cristalinas según las reivindicaciones 28 a 37 de la solicitud colombiana, es idéntico a lo revelado en las reivindicaciones 5 a 13 y 15 de la anterioridad WO 03/011278;

3.6. Por último, es también relevante resaltar que la solicitud colombiana en trámite en sus reivindicaciones 1, 2, 3, 4, 5, 7, 8, 10 y 11 se refiere simplemente a una distribución de tamaños de partícula de los cristales de escitalopram obtenidos, distribución que puede ser determinada a través de diversos métodos y equipos[1] (como microscopía óptica y tamización analítica) de amplio empleo en la industria farmacéutica y específicamente en etapas como las de preformulación y formulación tal como cualquier persona medianamente versada en la materia lo sabe.

Teniendo en cuenta todo lo expuesto hasta el momento, la solicitud colombiana en trámite no puede pretender ostentar el cumplimiento de los requisitos de patentabilidad, toda vez, que, su contenido y objetivos se encuentran consignados y expuestos en la solicitud internacional WO 03/03/011278 y que las aparentes diferencias con el arte anterior radican simplemente en un estudio de distribución de los tamaños de partícula (de uso común en la industria farmacéutica) y la separación de las impurezas que, obviamente, deberán ser retiradas para no afectar la calidad del producto, y que deberán atenderse en la etapa de preformulación, no solo por la formulación planteada en la solicitud colombiana, sino por cualquier formulación cuya eficiencia y eficacia dependan de las características del fármaco y excipientes, como son la forma, distribución y tamaño de partículas, y que se traduzcan en una adecuada compresión o granulación de dichos componentes.

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[1] Jose Luis Vila Jato. Dolores Ochoa. Esther Alegre. Juan Torrado. Tecnología Farmacéutica Aspectos

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16 y 18 de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Copia de la patente americana US 4,650,884 publicada el 17 de marzo de 1987.
- Copia de las páginas 1 a 6 y 10 a 15 de la patente británica GB 2 357 762 A.
- Copia de las columnas 1, 2, 3, 4, 5, 8 y capítulo reivindicatorio de la patente americana US 4,943,590
- Tecnología Farmacéutica: Aspectos fundamentales de los sistemas farmacéuticos y Operaciones Básicas. Volumen I, Parte 1, Capítulo 1, páginas 43 a 49.
- La publicación internacional WO 03/000672 publicada el 03 de Enero de 2003 y titulada "PROCESS FOR THE PREPARATION OF RACEMIC CITALOPRAM AND/OR S-CITALOPRAM BY SEPARATION OF A MIXTURE OF R- AND S-CITALOPRAM" páginas 1, 5, 6, 8, 14 y capítulo reivindicatorio.
- La solicitud internacional WO 03/011278 publicada el 13 de Febrero de 2003 y titulada "CRYSTALLINE COMPOSITION CONTAINING ESCITALOPRAM" paginas 1, 3, 4, 5, 6, 7, 8, 10 y capítulo reivindicatorio.

VI. ANEXOS

Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

1. Certificado de existencia y representación legal de Tecnoquímicas S.A y Lafrancol S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Constancia de pago para sustentar la solicitud de prórroga a que se refiere el artículo 42, inciso 2º de la Decisión 486.
5. Copia para correr traslado al solicitante.
6. El mencionado en el acápite de pruebas.

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Tecnoquímicas S.A., las recibirá en la secretaría de su Despacho o en su sede localizada en la Calle 23 # 7-39, de la ciudad de Cali y Lafrancol las recibirá en la secretaría de su Despacho o en su sede localizada la Carrera 1 No. 46-84 de la ciudad de Cali.

Señor Superintendente,

JOSÉ LUIS REYES VILLAMIZAR
C.C. 79'152.473 de Usaquén
T.P.A. 44.655 del C.S.J.

United States Patent [19]

Bogeso

[11] **Patent Number: 4,650,884**

[45] **Date of Patent: Mar. 17, 1987**

[54] **NOVEL INTERMEDIATE AND METHOD FOR ITS PREPARATION**

[75] Inventor: **Klaus P. Bogeso**, Lyngby, Denmark

[73] Assignee: **H. Lundbeck A/S**, Copenhagen-Valby, Denmark

[21] Appl. No.: **761,774**

[22] Filed: **Aug. 2, 1985**

[30] **Foreign Application Priority Data**

Aug. 6, 1984 [GB] United Kingdom 8419963

[51] **Int. Cl.**[4] **C07D 307/87**; C07C 121/80

[52] **U.S. Cl.** **549/467**; 558/422

[58] **Field of Search** ..... 260/465 E; 549/467; 558/422

[56] **References Cited**

U.S. PATENT DOCUMENTS

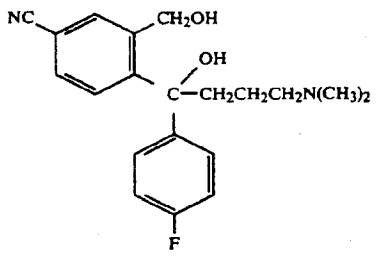
4,136,193 1/1979 Bogeso et al. 549/467

Primary Examiner—Dolph H. Torrence

Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

The present invention relates to the novel compound of the following formula:



I

as well as acid addition salts thereof, a method for the preparation of the compound of Formula I, and to the use of said novel compound in the preparation of the known antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, or a pharmaceutically acceptable acid addition salt thereof.

3 Claims, No Drawings

NOVEL INTERMEDIATE AND METHOD FOR ITS PREPARATION

BACKGROUND OF THE INVENTION

The preparation and properties of antidepressant substituted 1-dimethylaminopropyl-1-phenylphthalans (or 1-(3-dimethylaminopropyl)-1-phenyl-1,3-dihydroisobenzofurans) have been described in U.S. Pat. No. 4,136,193. The most interesting of these compounds contain a cyano-group, and one of these, 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, has shown great promise as a valuable antidepressant drug with few side effects.

It has been found, however, that the methods described in U.S. Pat. No. 4,136,193 for the preparation of this compound possess some problems in the scale-up to commercial production, and this has necessitated further research in an attempt to discover a shorter route to this compound and to avoid the risk involved in the metalation step used previously.

SUMMARY OF THE INVENTION

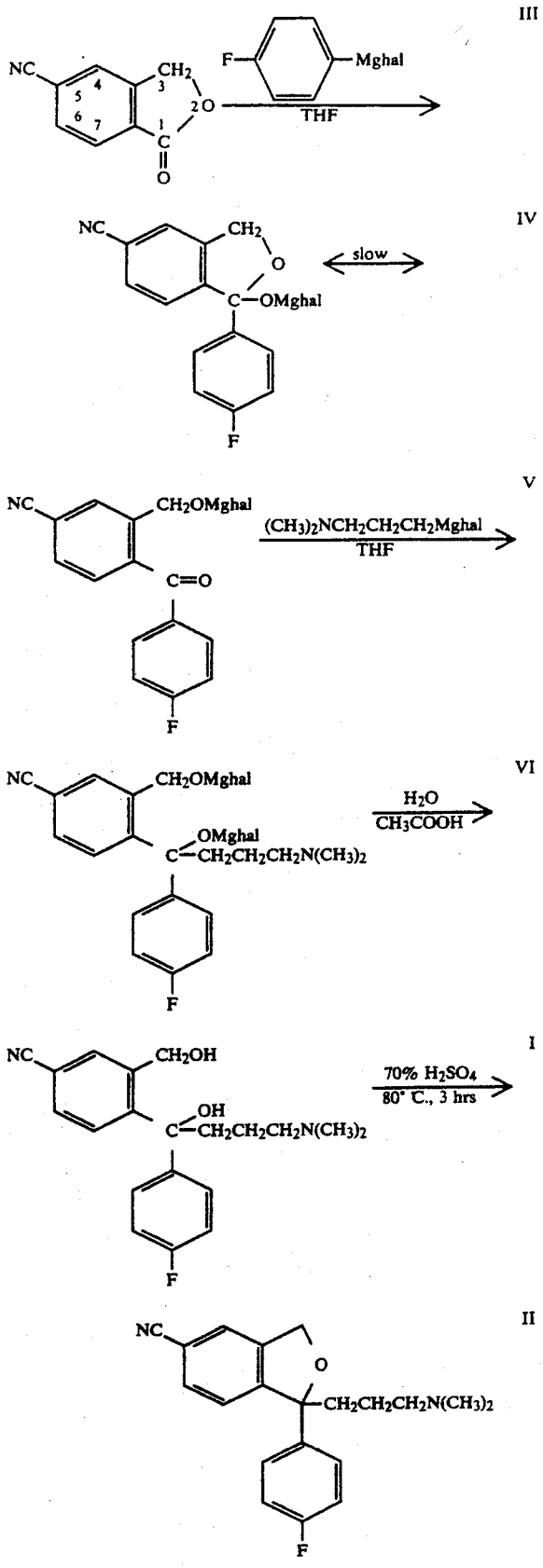
It is an established fact that the cyano-group of aromatic nitriles is very sensitive to attack by a number of organic as well as inorganic compounds (see for example "Methoden der Organischen Chemie", Houben-Weyl, Vol. 8, 345–51, 429, Georg-Thieme Verlag, Stuttgart (1952)).

For example, nitriles may be attacked by Grignard reagents to give ketimines which can be hydrolyzed to ketones. This method is a recommended standard method for preparation of ketones ("Methoden der Organischen Chemie", Houben-Weyl, Vol. 13/2a, 353–366, Georg-Thieme Verlag, Stuttgart (1973)). Actually, advantage of this invention has already been taken (as mentioned in U.S. Pat. No. 4,136,193) with molecules closely related to those of the present invention.

It is also wellknown that treatment of nitriles with strong acids such as high-percentage sulfuric acid normally will hydrolyze the nitrile-group to a carboxylic acid amide or a carboxylic acid.

The most useful method of preparation described in U.S. Pat. No. 4,136,193 involves Grignard reactions as well as treatment with strong acid, but the nitrile group was always introduced subsequent to such steps because of the known reactivity of the nitrile group described above. Typically, the cyano-group was introduced by reaction of a halogen substituted phthalane (as for example 1-(4'-fluorophenyl)-5-bromophthalane) with cuprous cyanide in DMF to yield a cyano-phthalane (as for example 1-(4'-fluorophenyl)-5-phthalanecarbonitrile) which was metalated and then alkylated through reaction with 3-dimethylaminopropyl chloride to yield the desired 1-(3-dimethylaminopropyl)-1-phenylphthalan, especially 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-5-phthalancarbonitrile.

According to the method of the present invention it has now surprisingly been found that cyano-substituted compounds can be prepared in good yields by the following route:



The compound of Formula II is the wellknown antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

The 5-cyanophthalide (Formula III) used as a starting material is a known compound (Tirouflet, J.; Bull.Soc.-Sci.Bretagne 26, 35, (1951).

In the formulas IV, V and VI "hal" means halogen, preferably chlorine or bromine. It is, indeed, surprising that only modest amounts of biproducts are formed by reaction of the cyano-group with the two Grignard-reagents involved. Of similar great importance to the success of this scheme is the surprisingly low rate of ring opening of the addition product formed in the first Grignard step (Formula IV). Actually, it is very convenient from a practical point of view to be able to run these two Grignard reactions in succession in the same vessel.

The novel intermediate (of Formula I) produced in the combined Grignard steps may be isolated and purified as described below. However, it is far more convenient to proceed with the ring closure of the crude material.

The cyano-group also shows a surprising resistance to the rather drastic and prolonged treatment with strong acid in the step of ring closure.

With careful control of the reaction conditions involved this process has already been shown to be very reliable on a technical scale as evidenced by smooth performance, stable yields and high purity of the final product (Formula II) produced.

The following examples are given by way of illustration only and are not to be construed as limiting;

EXAMPLE 1

4-[4-(Dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile

A Grignard solution is prepared by addition of 1-bromo-4-fluorobenzene (594 g, 3.4 mole) in dry tetrahydrofuran (1.6 liters) to a suspension of magnesium turnings (101 g, 4.15 mole) in dry tetrahydrofuran (250 ml) at reflux. When all has been added the solution is left stirring for 30 minutes without cooling or heating, and is then filtered to remove excess magnesium turnings. The Grignard solution is added to a nitrogen purged slurry of 5-cyanophthalide (450 g, 2.83 mole) in dry tetrahydrofuran (2.9 liters) in the course of 3 hours. The temperature is kept at 0°–3° C. during the addition after which the reaction mixture is stirred for 30 min. without cooling and then left standing overnight.

The same day a second Grignard solution is prepared from 3-dimethylaminopropyl chloride (342 g, 2.81 mol) and magnesium turnings (81 g, 3.3 mol) in dry tetrahydrofuran (1.15 liters). Next day the filtered solution of 3-dimethylaminopropylmagnesium chloride is added in the course of 6 hours to the reaction mixture obtained in the first Grignard reaction. The temperature is kept at 10°–12° C. during the addition whereupon the mixture is stirred for 30 minutes without cooling, and is then left overnight at room temperature without stirring. The reaction mixture is poured into icewater (2 kg ice, 3 liters water) whereupon acetic acid (700 ml, 80% by weight) is added, resulting in a final pH of 6.5–7.0 in the solution. Tetrahydrofuran is then distilled until a maximum pot temperature of 50° C. at 60 mm Hg is reached, whereupon toluene (4.5 liters) is added to the mixture. Aqueous ammonia (300 ml, 25% by weight) is then added to give a final pH of 9 in the water layer, the temperature is adjusted to 45°–50° C., and the mixture is stirred for 15 minutes. The toluene layer is separated, and the aqueous layer is extracted once with toluene (600 ml). The combined toluene extracts are washed with warm (50° C.) water (600 ml) and are then extracted with dilute acetic acid (2.5 liters water and 800 ml acetic acid, 80% by weight). The acetic extract is separated and combined with toluene (3.8 liters), whereupon aqueous ammonia (900 ml, 25% by weight) is added to give a final pH of 9 or higher in the water layer. The toluene phase is separated, and the water layer is extracted once with toluene (600 ml), whereupon the combined toluene extracts are washed four times with warm (50° C.) water (4×1 liter). This toluene solution is normally used directly in the next step.

If desired, the title compound can be isolated and purified in the following manner:

The warm toluene solution from above is stirred for 30 min. at 60° C. with charcoal (50 g) and silica gel (150 g, Merck Darmstadt No. 7734) and then filtered by suction on a filter pretreated with filter aid. This treatment is repeated with charcoal (25 g) and silica gel (90 g). After filtration the toluene is removed at reduced pressure (20 mm Hg) to a maximum of 60° C. The resulting oil (640 g) is dissolved in boiling diethyl ether (1500 ml) and this solution is stirred vigorously with water (1500 ml) while adding 47% aqueous hydrogen bromide (190 ml) during 10 min. at 27°–34° C. Diethyl ether is then distilled at reduced pressure at 33°–35° C. Additional water (500 ml) is added, and the mixture is cooled to 11° C. After 18 hours the crystals are collected on a suction filter. The wet cake is recrystallized from water (1500 ml) with the use of charcoal (37 g) and then dried for 23 hours in a vacuum oven at 50° C. and 220 mm Hg. Yield: 525 g of solid material which is purified further from a hot mixture of 2-propanol (9.5 liters) and ethanol (2.73 liters) with the use of charcoal (82 g) and silica gel (191 g) after which the filtrate is mixed with hexane (2 liters) and then cooled to 12° C. The crystals are isolated by suction and then dried in vacuum (200 mm Hg) at room temperature.

Yield of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)benzonitrile, hydrobromide: 425 g. MP 205°–206° C.

Elemental analysis ($C_{20}H_{23}FN_2O_2HBr$):

	Found	Calculated
% C	56.21	56.74
% H	5.69	5.73
% N	6.33	6.61
% Br	18.86	18.87

^{1}H-NMR (DMSO-d_6, Me_4Si as internal reference standard): 1.1–1.9 ppm (m, 2H, —CH_2—$\underline{CH_2}$—$\underline{CH_2}$N<), 2.1–2,45 ppm (broad t, 2H, >$\underline{COH}$—$\underline{CH_2}$—CH_2—), 2.6–2.8 ppm (s, 6H, —N($\underline{CH_3}$)$_2$), 2.85–3.2 ppm (broad t, 2H, —$\underline{CH_2}$N<), 3.85–4.75 ppm (broad q, 2H, —$\underline{CH_2}$OH), 5.0–5.4 ppm (broad s, 1H, —$\underline{OH}$), 5.8–6.2 ppm (broad s, 1H, —$\underline{OH}$), 6.95–7.5 ppm (m, $\underline{4H}$, aromatic), 7.7–8.0 ppm (m, $\underline{3H}$, aromatic), 9.0–9.75 (broad s, $\underline{1H}$,

HPLC-analysis (Spherisorb S 5 W; Mobile phase: Heptane-propanol-2-aqueous ammonia-H_2O,

85:15:0.4:0.2, UV_{254} detector) showed a content of 99.6% of the title compound.

EXAMPLE 2

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide

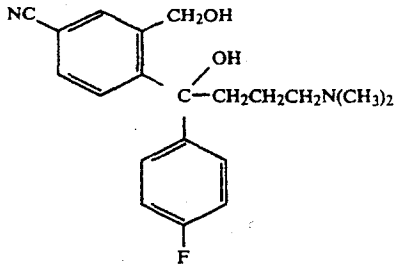
The toluene solution containing the crude product mentioned in Example 1 is heated to 50° C., and 70% sulfuric acid (made from 321 g of 96% sulfuric acid and 119 g ice) is added while stirring. The mixture is heated to 80° C. and kept at this temperature for 3 hours, whereupon it is cooled to about 30° C. Cold water (600 ml) and aqueous ammonia (600 ml, 25% by weight) are then added, and the mixture (pH 10) is stirred at 50°–60° C. for 15 minutes. The water phase is discarded, and the toluene layer is washed 5 times with warm water (5×1 liter). The organic phase is dried over anhydrous sodium sulfate, filtered and stirred for 1 hour with silica gel (375 g). The mixture is filtered by gravity on a filter precharged with silica gel (188 g). The filter is rinsed with toluene (3.4 liters) and the combined filtrates are evaporated under reduced pressure (30 mm Hg) until a maximum temperature of 50° C. is reached. The residue is then dissolved in acetone (2 liters) and filtered with charcoal. The filtrate is cooled to 20° C. Gaseous hydrogen bromide (130–140 g) is then introduced during 2 hours at 20°–25° C. until pH is 3, and pH is then adjusted to 7 by adding some of the acetone solution of the title compound. The mixture is left crystallizing overnight whereupon the crystals are filtered and washed with hexane (750 ml) and then with acetone (750 ml). After drying at 45° C. a yield of 610–650 g crude title compound is obtained. This material is dissolved in water (1.8 liters) at about 55° C. and is then filtered with charcoal, cooled to 20° C. and left overnight for crystallization after addition of seed crystals. The crystals are filtered, washed with water (350 ml) and dried. Yield: 560–570 g.

The crystals from the 1st recrystallization are dissolved in a mixture of methanol (1.7 liters) and 2-propanol (3.4 liters) at 70° C., and are then filtered with charcoal, cooled to 20° C. and left for crystallization overnight. The crystals are filtered and washed with a mixture of methanol (150 ml) and 2-propanol (300 ml). After drying there is obtained 510–520 g of purified material.

The material from the 2nd recrystallization is dissolved in a mixture of methanol (510 ml) and acetone (2.04 liters) at 55° C. and is then filtered with charcoal. The filtrate is cooled to 20° C., and after addition of seed crystals hexane (4.1 liters) is slowly added during 1 hour. After crystallization overnight the crystals are filtered and washed first with a mixture of acetone (150 ml) and hexane (300 ml), and then washed two times with hexane (2×300 ml). After drying there is obtained 470–480 g of pure (1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, hydrobromide, MP 185°–186° C.

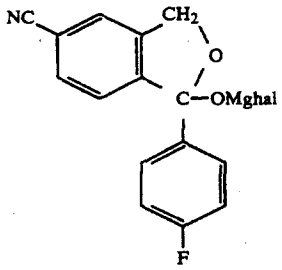
I claim:

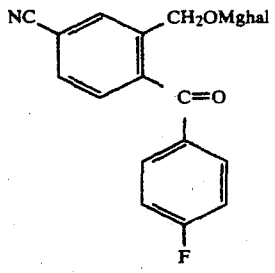
1. A compound of the following formula:



or an acid addition salt thereof.

2. A method for the preparation of a compound of claim 1, characterized thereby that 5-cyanophthalide is reacted with a Grignard solution containing a 4-fluorophenyl magnesium halide, whereupon the resulting mixture containing the compounds of the following structures in equilibrium





is reacted with a Grignard solution containing a 3-dimethylaminopropyl magnesium halide, the reaction mixture hydrolyzed and the resulting 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile isolated as the free base, or an acid addition salt thereof.

3. In a method for the preparation of the compound 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile, or a pharmaceutically-acceptable acid addition salt thereof, the step of effecting ring-closure by dehydration of a compound of claim 1 by reacting the same with strong sulfuric acid.

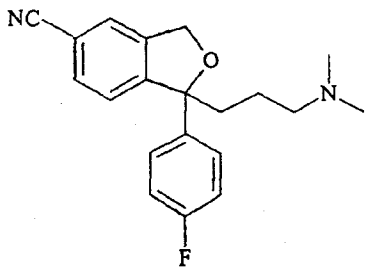
* * * * *

Crystalline Base of Citalopram

The present invention relates to the crystalline base of the well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile, formulations of said base, a process for the preparation of purified salts of citalopram, such as the hydrobromide, using the base, the salts obtained by said process and formulations containing such salts.

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



(I)

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982,** *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75* , 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

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 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). Citalopram is marketed as the hydrobromide and the hydrochloride, respectively.

A number of processes for the preparation of citalopram have been disclosed. In many of these, the last step of the process is a conversion of a group different from cyano in the 5 position of the direct analogue of citalopram to a 5-cyano group. So citalopram has been prepared by:

Exchange of 5-halogen, or 5-CF_3-$(CF_2)_n$-SO_2-O- with cyano (DE 2,657,013 and co-pending WO 0011926 and WO 0013648)

Conversion of a 5-amido or 5-ester group to a 5-cyano group (WO 9819513)

Conversion of a 5-amino group to a 5-cyano group (WO 9819512)

Conversion of a 5-formyl group to a 5-cyano group (WO 9900548)

Conversion of a 5-oxazolinyl or 5-thiazolinyl group to a 5-cyano group (WO 0023431)

Other processes for the preparation of citalopram comprise exchange of the 5-bromo group of 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide with 5-cyano followed by alkylation with a 3-(N,N-dimethylamino)propyl-halogenide (DE 2,657,013 and WO 9819511).

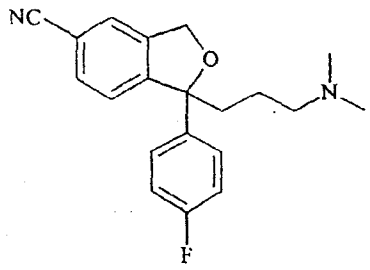
Many of the processes mentioned above have the disadvantage that it is difficult to separate the intermediates formed during the process (the intermediates mentioned above or earlier intermediates) from the end product and, accordingly, extensive purification procedures involving loss of citalopram are required in order to obtain the necessary quality of the end product.

It has now been found that the base of citalopram may be obtained as a very nice and pure crystalline product, which may easily be handled and conveniently be formulated into tablets and other pharmaceutical forms. Furthermore, it has surprisingly been found that a very good and efficient purification of citalopram may be obtained during manufacture of citalopram (e.g. of the hydrobromide or the hydrochloride salt) by crystallising the base, and thereafter optionally forming a salt from the base.

This purification process is particularly useful for removing intermediates which are structurally closely related to citalopram, in particular compounds which only differ from citalopram by the substituent situated in position 5 on the isobenzofurane ring, and intermediates which have physical/chemical properties which are close to those of citalopram, e.g. the 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuranes having halogen (in particular bromide and chloride), an amide or an ester in position 5 of the isobenzofurane ring, or 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide, or -cloride.

Summary of the invention

The present invention provides the crystalline base of the compound



(I)

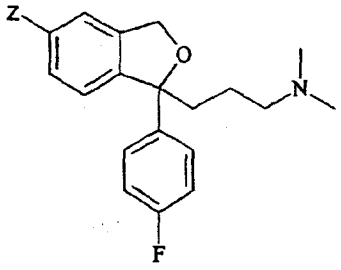
In a second aspect, the invention provides a process for the manufacture of a salt of citalopram, preferably the hydrobromide or hydrochloride in which the free base of citalopram is precipitated in crystalline form, optionally re-crystallised one or more times and then transferred to a pharmaceutically acceptable salt of citalopram.

In a further aspect, the invention relates to the pure crystalline salt, preferably the hydrobromide or hydrochloride prepared by the process of the invention.

In particular, the invention relates to a process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free and precipitated in crystalline form, optionally re-crystallised one or more times, and then transferred into a salt thereof.

In particular, the invention relates to a process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free from a crude salt or crude mixture of citalopram.

More particularly, the present invention relates to a process for the manufacture of citalopram base or a salt of citalopram characterised in that one or more impurities of the formula



(II)

wherein Z is halogen, $-O-SO_2-(CF_2)_n-CF_3$, where n is 0-8, -CHO, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of

citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof.

The crude mixture of citalopram containing the compound of formula II as an impurity may be prepared by subjecting a compound of formula II to a cyanide exchange reaction with a cyanide source, or by subjecting 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranhalogenide, in particular the bromide, to a cyanide exchange reaction followed by alkylation with a 3-(N,N-dimethylamino)propyl-halogenide.

In a particular embodiment of the invention, Z is halogen, in particular bromide or chloride.

In a particularly preferred embodiment of the invention, the salt prepared is the hydrobromide or hydrochloride salt of citalopram.

The crude salt may be any convenient salt, such as the hydrobromide, hydrochloride, sulphate, oxalate, phosphate, nitrate or any other convenient salt. Other salts are salts of organic acids.

In a preferred embodiment of the invention, the crude salt is the sulphate, the hydrobromide or the hydrochloride salt.

The invention also relates to a hydrochloride or hydrobromide salt of citalopram prepared by the processes of the invention. In particular, the invention relates to a hydrochloride or hydrobromide salt of citalopram having a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

In yet another aspect, a pharmaceutical formulation of the free base of citalopram, or a hydrobromide or hydrochloride prepared from said base, is provided. Preferably the formulation is for oral administration.

The formulations according to the invention may be prepared by direct compression of citalopram in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of citalopram, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

In particular, the pharmaceutical composition of the invention contains the racemic mixture of citalopram base, citalopram hydrochloride or citalopram hydrobromide.

The crystalline base of citalopram is preferably more than 99.8% w/w pure, most preferably more than 99.9% w/w pure (peak area). The melting point is preferably a range within 90 – 93 °C, most

preferably 91 - 92 °C (DSC; onset, open capsule) or it is between 92 and 94°C, preferably 92.5 and 93.5 °C (DSC; onset, closed capsule). The crystalline base of citalopram is preferably in racemic form.

The terms "crude salt" and "crude mixture" refer to the fact that the salt and the mixture, respectively, comprise impurities, in particular impurities of formula II, which must be removed or which it is desired to remove.

The crude salt may be a salt separated directly from the reaction mixture, or the crude reaction mixture may have been subjected to some initial purification, e.g. one re-crystallisation, and /or treatment with activated carbon or silica gel, and the salt formed subsequently by treatment with an acid using methods known in the art. The salt may be isolated by precipitation or it may exist in a solvent, e.g. in the mixture resulting directly from the synthesis of the salt.

Similarly, the crude mixture comprising citalopram may be obtained directly from the synthesis of the compound according to any of the above mentioned processes or it may have been subjected to some initial or simultaneous purification, e.g. one re-crystallisation, treatment with activated carbon or silica gel.

The base of citalopram may be set free from the crude salt by dissolving the crude salt in a mixture of water and an organic solvent and then adding a base. The organic solvent may be toluene, ethyl acetate or any other suitable solvent and the base may be any convenient base, preferably NaOH or NH_3. Likewise, the base of citalopram may, if necessary, be set free from a crude mixture containing citalopram by treatment with a base.

Crude mixtures containing citalopram base may be subjected to further purification and extraction, before the base is precipitated in crystalline form. The base of citalopram may be isolated by separation of the organic phase, evaporation of the solvent in order to obtain the base most probably as an oil and then crystallisation of the base from an aprotic solvent, such as an alkane, including n-heptane, hexane and isooctane, and high and low boiling petroleum ethers and substituted aromates, incl toluene and xylenes. Crystalline citalopram base may be re-crystallised from the same solvents.

The pharmaceutically acceptable salt of citalopram, such as the hydrobromide or hydrochloride, may be prepared by methods known in the art. So, the base may be reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously. The

hydrobromide or hydrochloride of citalopram obtained by the method of the invention has a very high purity, preferably more than 99,8% pure, most preferably more than 99,9 % purity. Other salts of citalopram, e.g. the oxalate, may also be obtained in a very pure form by this process.

The cyanide exchange reactions mentioned above may be carried out as described in the patent applications mentioned above.

In particular, when Z is halogen, or CF_3-$(CF_2)_n$-SO_2-O- wherein n is an integer in the range 0-8, incl., the conversion to a cyano group may be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, $Zn(CN)_2$ or $(R^4)_4NCN$ where R^4 indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched alkyl, in the presence of a palladium catalyst and a catalytic amount of Cu^+ or Zn^{2+}, or with $Zn(CN)_2$ in the presence of a palladium catalyst.

The cyanide source is used in a stoichiometric amount or in excess, preferably 1-2 equivalents are used pr. equivalent starting material. R^4N^+ may conveniently be $(Bu)_4N^+$. The cyanide compound is preferably NaCN or KCN or $Zn(CN)_2$.

The palladium catalyst may be any suitable Pd(0) or Pd(II) containing catalyst, such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh)_2Cl_2$, etc. The Pd catalyst is conveniently used in an amount of 1-10, preferably 2-6, most preferably about 4-5 mol%.

Catalytic amounts of Cu^+ and Zn^{2+} , respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 %. Conveniently, about ½ eq. is used per eq. Pd . Any convenient source of Cu^+ and Zn^{++} may be used. Cu^+ is preferably used in the form of CuI and Zn^{2+} is conveniently used as the $Zn(CN)_2$ salt.

When Z is Br or I, the conversion to a cyano group may also be carried out by reaction with Cu(CN) without catalyst. In a preferred embodiment, the reaction is performed at elevated temperature.

In another aspect of the invention, the reaction is performed in an ionic liquid of the general formula $(R^5)_4N^+$, X^-, wherein R^5 are alkyl-groups or two of the R^5groups together form a ring and X^- is the counterion. In one embodiment of the invention, $(R^5)_4N^+X^-$ represents

In particular, the formulations according to the invention may be prepared by direct compression of citalopram in admixture with conventional adjuvants or diluents. Alternatively, a wet granulate or a melt granulate of citalopram, optionally in admixture with conventional adjuvants or diluents may be used for compression of tablets.

Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilisation of the solution and filling in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

According to the present invention, the base of citalopram has been found to be crystalline with stable and nice white crystals and it has been found that the base may easily be crystallised in a very pure form. So for example more than 99.8% w/w pure citalopram base was obtained by crystallisation from up to 95% pure hydrobromide without further purification. Accordingly, the process of the invention for preparing salts of citalopram has been found to give the salts as very pure products of pharmaceutically acceptable quality. Accordingly, the yield may be improved substantially during the manufacture of citalopram.

Finally, it has been found that the crystalline citalopram base may be formulated into very good and stable solid formulations with good release properties.

The invention is further illustrated by the following examples.

Example 1

Crystallisation of R,S-Citalopram as the free base.

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile.

1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrobenzofuran-5-carbonitrile hydrobromide (101 grams, 0.25 mole) prepared from 1-(3-Dimethylaminopropyl)- 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuranbromide, 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 (2x100 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 form. The white crystals of the title compound are filtered off and dried at ambient temperature over night in vacuo. Yield: 75.4 grams (93%). DSC(onset, open capsule): 91.3-91.8 °C DSC (onset, closed capsule): 92.8 °C. Purity: (> 99.8 % (peak area)).

Anal. calcd. for C20H21N2F1O1; C, 74.04; H, 6.54; N, 8.64. Found C, 74.01; H, 6.49; N, 8.59. 1H-NMR (DMSO-d6 , 500 MHz): 1.21 (1H, m), 1.29 (1H, m), 2.02 (6H, s), 2.09-2.23 (4 H, m), 5.15 (1H, d J=12.5 Hz), 5.22 (1H, d J=12.5 Hz), 7.16 (2H, t J=8.5 Hz), 7.60 (2H, dt J=8.5 Hz J=1.2 Hz), 7.76 (1H, d J= 8.5 Hz), 7.79 (1H, d J=8.5 Hz), 7.80 (1H, s). 13C-NMR (DMSO-d6 , 125 MHz): 21.8, 38.3, 45.0, 58.8, 71.0, 90.7, 110.5, 115.1 (d J=22 Hz), 118.8, 123.1, 125.1, 127.0 (d J=8 Hz), 132.0, 140.0 (d J=3 Hz), 140.5, 149.5, 161.3 (d J=245Hz).

Example 2

a) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene is evaporated and the citalopram base obtained is dissolved in n-heptane at elevated temperature. The very pure free base of citalopram is precipitated by cooling.

b) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene is evaporated and the citalopram base obtained is dissolved in methanol. The mixture is treated with activated carbon and filtrated and the solvent is evaporated. The purified free base is dissolved in n-heptane at elevated temperature. Then the very pure free base of citalopram is precipitated by cooling.

c) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene phase is treated with silicagel, the toluene is evaporated and the citalopram base obtained is dissolved in n-heptane at elevated temperature. The very pure free base of citalopram is precipitated by cooling.

d) A crude mixture of Citalopram and sulphuric acid is made basic by adding NaOH and the citalopram base is extracted with toluene. The toluene phase is treated with silicagel, the toluene is evaporated and the citalopram base obtained is dissolved in methanol. The mixture is treated with activated carbon and filtrated and the solvent is evaporated. The purified free base is dissolved in n-heptane at elevated temperature. Then the extremely pure free base of citalopram is precipitated by cooling.

Example 3

Wet granulation and preparation of tablets

The batch size was 200 g and the granulation was performed in a small-scale laboratory high shear mixer (Micromixer).

Citalopram base was sieved through a sieve aperture of 0.3 mm. The ingredients of the intragranular phase (1 - 4 in Table 1) were mixed at 600 rpm. 25 ml of purified water (5) was added in 30 sec and the granulation terminated after a total processing time of 3 min. The granulate was wet sieved through a 0.7 mm sieve aperture and dried at 40 °C in 30 minutes to equilibrium relative humidity of 32 %. The dried granulate was finally sieved through a 0.7 mm sieve aperture.

The dried granulate was mixed for 3 minutes with the extragranular phase (6 – 7) in a Turbula mixer and finally mixed with the lubricant (8) for 30 sec.

	Materials	%
1	Citalopram (base)	16.00
2	Kollidon VA64	2.32
3	Lactose 350 mesh	38.98
4	Corn starch	20.00
5	Purified water	25
6	Avicel PH 200 (Microcrystalline cellulose)	20.00
7	Ac-Di-Sol (Croscarmelose sodium)	2.00
8	Magnesium stearate	0.7

Table 1. Composition of the tablets.

Tablets were produced on a single punch tabletting machine Korsch EK0. The characteristics of the tables are shown in Table 2.

Parameter	Values
Tablet strength, mg	20
Nominal tablet weight, mg	125
Tablet diameter, mm	7
Tablet shape	Film coating (special doomed)
Mean disintegration time, min	1.77
Mean chrushing strength, N	69.1
Mean tablet weight, mg	125.4
RSD tablet weight, %	0.42
Friability, %	0.3

Table 2. Tablet characteristics.

The tablets produced had satisfactory technical properties.

Example 4

Melt granulation

The batch size was 200 g. Citalopram base was sieved through a sieve aperture of 0.3 mm. The granulation was performed in a small-scale laboratory high shear mixer (Micromixer)

The ingredients of the intra-granular phase (1 - 3 in Table 3) were mixed at 1200 rpm. The jacket temperature was 80 °C. The granulation process was terminated after 3.5 min. The granulate was sieved through a sieve aperture of 1.0 mm and mixed with the extra-granular phase (4, 5) for 3 min. and with the lubricant (6) for 30 sec.

	Materials	%
1	Citalopram (base)	16.00
2	Polyethyleneglycol 6000	9.14
3	Lactose 350 mesh	38.98
4	Avicel PH 200 (Microcrystalline cellulose)	30.00
5	Kollidon CL (Cross-linked povidone)	4.00
6	Magnesium stearate	0.7

Table 3. Composition of the tablet.

Tablets were produced on a single punch tabletting machine Korsch EK0. The characteristics of the tables are shown in Table 4.

Parameter	Values
Tablet strength, 20 mg	20
Nominel tablet weight, mg	125
Tablet diameter, mm	7
Tablet shape	Film coating , Special doomed
Mean disintegration time, min	1.0
Mean chrushing strength, N	55.5
Mean tablet weight, mg	125.6
RSD tablet weight, %	0.5
Friability, %	0.4

Table 4. Tablet characteristics.

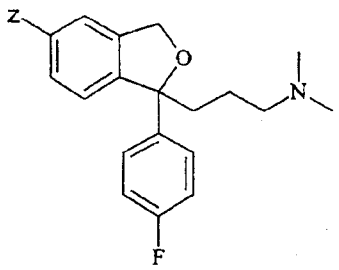
The tablets produced had satisfactory technical properties.

CLAIMS

1. A process for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free and precipitated in crystalline form, optionally re-crystallised one or more times, and then transferred into a salt thereof.

2. The process of Claim 1 for the manufacture of a salt of citalopram characterised in that the base of citalopram is set free from a crude salt or a crude mixture of citalopram.

3. A process for the manufacture of citalopram base or a salt of citalopram characterised in that one or more impurities of the formula



(II)

wherein Z is halogen, $-O-SO_2-(CF_2)_n-CF_3$, where n is 0-8, -CHO, $-NHR^1$, $-COOR^2$, $-CONR^2R^3$ wherein R^2 and R^3 are selected from hydrogen, alkyl, optionally substituted aryl or aralkyl and R^1 is hydrogen or alkylcarbonyl, are removed from a crude mixture of citalopram or from a crude salt of citalopram, by precipitating citalopram base in crystalline form, optionally re-crystallising said base one or more times and/or transferring said base into a salt thereof.

4. The process according to Claim 3 wherein the crude mixture of citalopram containing the compound of formula II as an impurity, is prepared by subjecting a compound of formula II to a cyanide exchange reaction with a cyanide source.

5. The process according to Claim 3, wherein Z is halogen, in particular bromide or chloride.

6. The process according to Claims 3 to 5 wherein the crude mixture of citalopram is subjected to initial purification before the base of citalopram is precipitated in crystalline form.

7. The process according to Claims 3 to 5 wherein the crude mixture of citalopram is subjected to initial purification before a crude salt is formed from said crude mixture.

8. The process according to Claims 3 to 7 wherein the base of citalopram is set free from a crude salt or a crude mixture of citalopram by treatment with a base and optionally subjected to further purification before the base of citalopram is precipitated in crystalline form.

9. The process according to any of Claims 1 to 8 characterised in that the citalopram base is transferred into the hydrobromide or the hydrochloride salt of citalopram.

10. The process according to any of Claims 2-3, characterised in that the crude salt is a hydrobromide, hydrochloride, sulphate, oxalate, phosphate or nitrate salt, preferably the sulphate hydrobromide, or hydrochloride salt.

11. A crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram, characterised in that it has a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

12. The crystalline base of citalopram, or a hydrochloride or hydrobromide salt of citalopram prepared by the process of any of Claims 1-10.

13. The base, the hydrochloride or the hydrobromide salt of claim 12 characterised in that it has a purity of more than 99.8 %w/w, preferably more than 99.9 %w/w.

14. A pharmaceutical composition containing the hydrochloride or the hydrobromide salt of citalopram according to Claims 11 to 13, or the crystalline base of citalopram.

15. A pharmaceutical composition according to Claim 14 which is a tablet prepared by

a) direct compression of citalopram, optionally in admixture with pharmaceutically acceptable adjuvants;

b) by compression of a wet granulate of the citalopram, optionally in admixture with pharmaceutically acceptable adjuvants; or

c) by compression of a melt granulate of the citalopram, optionally in admixture with pharmaceutically acceptable adjuvants.

16. The pharmaceutical composition according to Claims 14 to 15 characterized in that it contains the racemic mixture of citalopram base, citalopram hydrochloride or citalopram hydrobromide.

United States Patent [19]

Boegesoe et al.

[11] **Patent Number: 4,943,590**

[45] **Date of Patent: Jul. 24, 1990**

[54] **PHARMACEUTICALLY USEFUL (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-FLUOROPHENYL)-1,3-DIHYDROSOBENZOFURAN-5-CARBONITRILE AND NON-TOXIC ACID ADDITION SALTS THEREOF**

[75] Inventors: **Klaus P. Boegesoe**, Lyngby; **Jens Perregaard**, Jaegerspris, both of Denmark

[73] Assignee: **H. Lundbeck A/S**, Copenhagen-Valby, Denmark

[21] Appl. No.: **363,589**

[22] Filed: **Jun. 8, 1989**

[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[5] **A61K 31/34**; C07D 307/87

[52] **U.S. Cl.** **514/469**; 558/422; 549/467

[58] **Field of Search** 549/467; 558/422; 514/469

[56] **References Cited**

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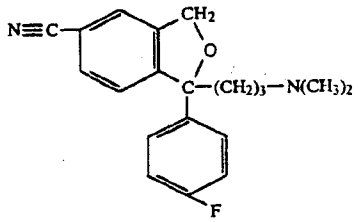
Primary Examiner—Mary C. Lee
Assistant Examiner—Bernard I. Dentz
Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

The two enantiomers of the anti-depressant drug of the formula I

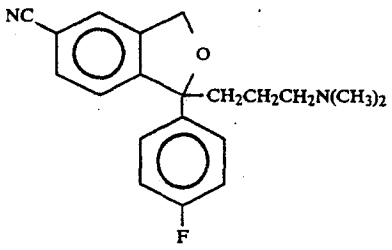


are disclosed. Methods for resolving intermediates and their steroselective conversion to a corresponding enatiomer of I are also disclosed.

12 Claims, No Drawings

PHARMACEUTICALLY USEFUL (+)-1-(3-DIMETHYLAMINOPROPYL)-1-(4'-FLUOROPHENYL)-1,3-DIHYDROSOBENZOFURAN-5-CARBONITRILE AND NON-TOXIC ACID ADDITION SALTS THEREOF

The present invention relates to the two novel enantiomers of the antidepressant drug 1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydrosisobenzofuranb 5-carbonitrile (citalopram) of the following formula I:



I

and to the use of these enantiomers as antidepressant compounds as well as the possible use as geriatrics or in the cure of obesity or alcoholism.

This invention also includes pharmaceutically acceptable salts of the enantiomers of compound I formed with non-toxic organic or inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in an aqueous miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling or an excess of the acid in aqueous immiscible solvent, such as ethyl ether, ethyl acetate or dicloromethane, with the desired salt separating directly. Exemplary of such organic salt are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, oxalic, salicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-amino-benzoic, glutamic, benzene sulfonic and theophylline acetic acid, as well as the 8-halotheophyllines, for example 8-bromotheophylline.

Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the conventional method of double decomposition of appropriate salts, which is well-known to the art.

Furthermore it was found that non-hygroscopic acid addition salts might be obtained by conventinal freeze drying techniques from water solutions of appropriate salts of the above mentioned kinds.

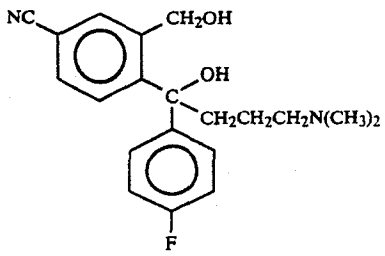
The invention is also concerned with a method to resolve the intermediate racemate and to produce the individual isomers of I therefrom.

BACKGROUND OF THE INVENTION

Citalopram, which has been disclosed in e.g. U.S. Pat. No. 4,136,193, has proven to be an efficient antidepressant compound in man (Ref.: A. Gravem et al., Acta pysychiat. Scand., No. 75, p. 478–486 (1987). All work in the development of this compound has been made with the racemate. Citalopram has been shown pharmacologically to be a very selective inhibitor of 5-HT reuptake. Previous attempts to crystallize diastereomeric salts of citalopram enantiomers have failed.

SUMMARY OF THE INVENTION

Surprisingly, it has now proven possible to resolve the intermediate 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, II, into its enantiomers and finally in a stereoselective way to convert these enantiomers to the corresponding citalopram enantiomers. Likewise, monoesters of II formed by optically active carboxylic acids could be separated into the corresponding diastereomers and subsequently converted directly into citalopram enantiomers in a stereoselective ringclosure reaction. The intermediate diol, II, has been disclosed in e.g. U.S. Pat. No. 4,650,884 as a racemic mixture.



II

The enantiomers of the intermediate of formula II as well as monoesters fall likewise within the scope of the present invention.

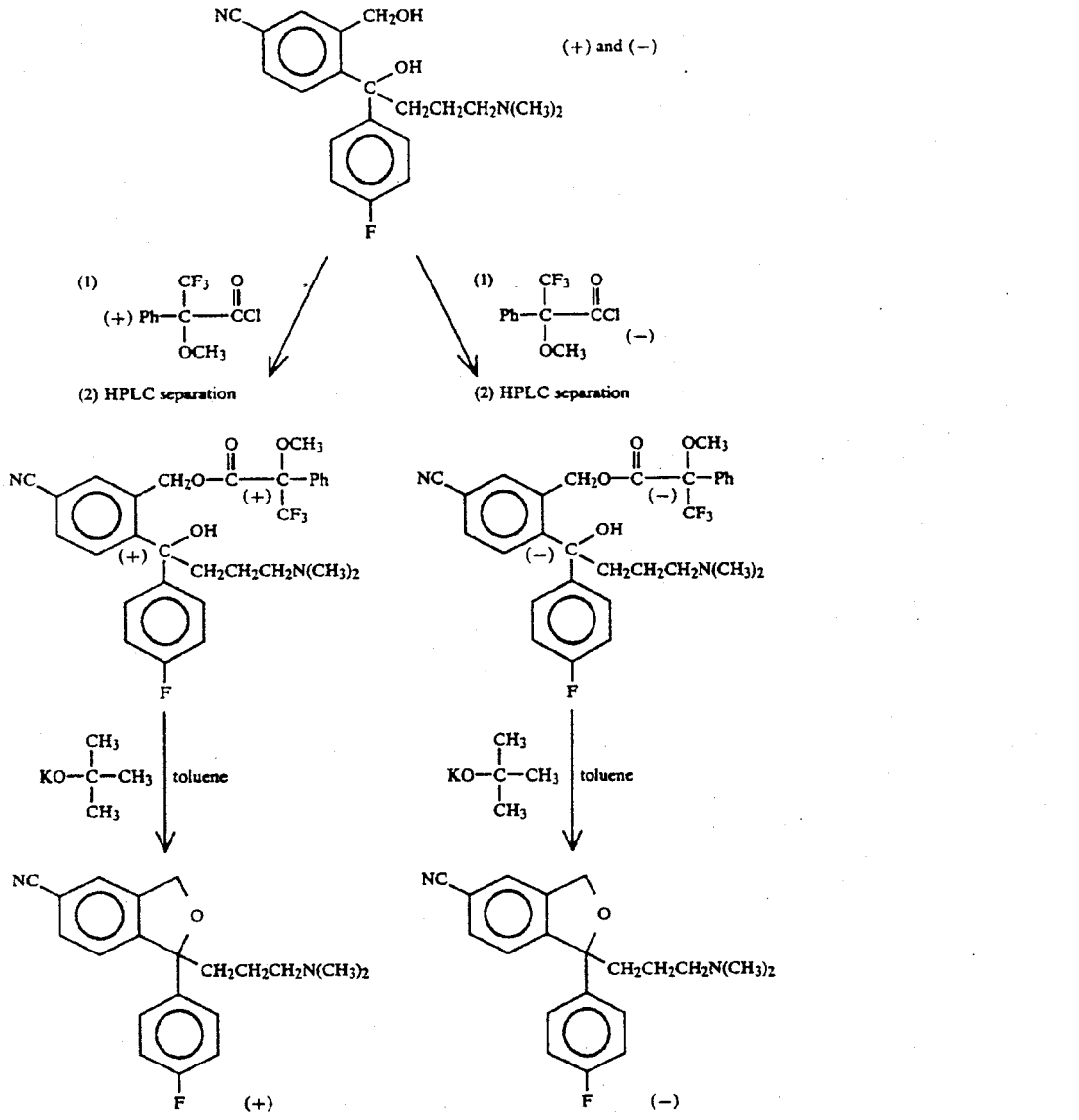
Furthermore, it was shown to our surprise that almost the entire 5-HT uptake inhibition resided in the (+)-citalopram enantiomer.

The present invention also includes a new method of synthesizing I from the diol compound II by esterification of the primary alcohol group into a labile ester, which in the presence of a base undergoes spontaneous ringclosure to citalopram or, if enantiomerically pure II is esterified, the corresponding citalopram enantiomer is produced with fully conservation of stereoconfiguration.

According to the invention, II is reacted with:

(a) an enantiomerically pure acid derivative as an acid chloride, anhydride or libile ester as e.g. examplified in reaction scheme I by (+)- or (−) -α-methoxy-α-trifluoromethylphenylacetyl chloride. The reaction is preferably performed in an inert organic solvent as e.g. toluene, dichloromethane or tetrahydrofuran. A base (triethylamine, N,N-dimethylaniline, pyridin or the like) is added to neutralize liberated HCl. The diastereoisomers are subsquently separated by HPLC or fractional crystallization. The thus purified disatereoisomers are finnaly separately treated with strong base (e.g. alkoxide) in an inert organic solvent as e.g. toluene, tetrahydrofuran, or dimethoxyethane yielding the pure citalopram enantiomers respectively. The ringclosure reaction is preferably performed at relatively low temperatures (−20° C.) to room temperature).

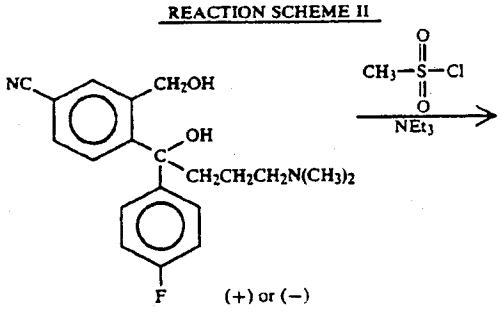
REACTION SCHEME I



(b) the enantiomers of an optically active acid successively affording the pure diastereomeric salts. Optically antipodes of tartaric acid, di-benzoyltartaric acid, di-(p-toloyl)tartaric acid, bisnaphthylphosphoric acid, 10-camphorsulphonic acid and the like are conveniently used.

(c) Stereoselective ringclosure of the pure enantiomers of II prepared as in (b) is performed via a labile ester as e.g. methansulfonyl, p-toluenesulfonyl, 10-camphorsulfonyl, trifluoracetyl or trifluoromethansulfonyl with simultaneous addition of a base (triethylamine, dimethylaniline or pyridin) in an inert organic solvent at 0° C. The ringclosure reaction is examplified in reaction scheme II:

REACTION SCHEME II



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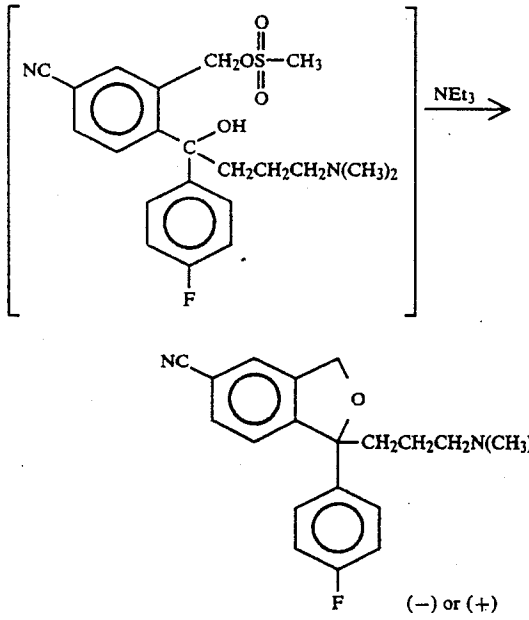
REACTION SCHEME II



EXAMPLE 1

Resolution by method (a)

To 11 g of (+)-α-methoxy-α-trifluoromethylacetic acid dissolved in 25 ml of chloroform were added 50 ml of thionylchloride and a few drops of dimethylformamide. The reaction mixture was refluxed for 2 hours. Excess of thionylchloride was evaporated with toluene leaving the (+)-α-methoxy-α-trifluoromethylacetyl chloride as a liquid. This liquid diluted with 50 ml of dichloromethane was added dropwise to an ice cooled solution of 17 gr of 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-hydroxybutyl)-3-(hydroxymethyl)-benzonitrile, II, and 8 ml of triethylamine in 150 ml of dichloromethane. The reaction mixture was further stirred for another hour at room temperature, subsequently washed with brine, dried ($MgSO_4$) and the solvent evaporated below 30° C. in vacuo affording 29 gr of the ester as a diastereomeric mixture. By repeated HPLC purification (eluted with ethyl acetate/tetrahydrofuran 9:1 containing 4% of triethylamine) and by collecting only the 5–10% initial substance in the main peak, 1.1 gr of enantiomerically pure compound was isolated.

The substance thus isolated was dissolved in dry toluene (50 ml) and added to a suspension of 0.3 gr of potassium t-butoxide in 20 ml of toluene at 0° C. The toluene solution was washed with water, dried ($MgSO_4$) and the solvent evaporated yielding 0.6 gr of (+)-1-(dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile as an oil. $[\alpha]_D = +11.81°$ (c=1, CH_3OH) (determined with a substance containing 10% w/w of methanol). The optical purity was determined by ^1H NMR spectroscopy ($CDCL_3$ as solvent) (Bruker AC-250 MHz instrument) by addition of a 10:1 w/w surplus of the chiral reagent (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol. Optical purity: 99.6%.

In a totally analogous way the (−)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile was synthesized. $[\alpha]_D = -12.34°$ (c=1, CH_3OH) (determined with a substance containing 10% w/w of methanol). Optical purity: 99.9%.

EXAMPLE 2

Resolution by methods (b) and (c)

To a solution of 85 gr of 4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile, hydrobromide in 500 ml of water were added 200 ml of ice cooled 2M NaOH solution and 500 ml of ether. The mixture was stirred for ½ hour, the ether phase separated, dried ($MgSO_4$) and the ether evaporated. The remaining oil was dissolved in 400 ml of 2-propanol at 40° C., and 40 gr of (+)-di-p-toloyltartaric acid (as hydrate) were added under vigorous stirring. After a short while crystallization began. After 3 hours of stirring the precipitated salt was filtered off and dried yielding 29.2 gr (55.1%) of (−)-4-(4-dimethylamino)-1-(4'fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benzonitrile, hemi (+)-di-p-toloyltartaric acid salt. MP: 134°–135° C., $[\alpha]_D = +10.0°$ (c=1, CH_3OH). The filtrate is used below.

To an ice cooled solution of 14 gr of the (−)-isomer from above as a base in 300 ml of dry toluene were added 16 ml of triethylamine, and 3.6 ml of methansulfonyl chloride in 20 ml of dry toluene were added dropwise during 10 minutes. The reaction mixture was further stirred for ½ hour, washed with brine, dried ($MgSO_4$) and the solvent evaporated. The title compound was purified by column chromatography affording 8 g of (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = +12.33°$ (c=1, CH_3OH). The oxalic acid salt of the (+)-isomer crystallized from acetone. MP: 147°–148° C., $[\alpha]_D = +12.31°$ (c=1, CH_3OH).

The pamoic acid salt of the (+)-isomer was prepared in the following manner: To 1.8 g of the base of the (+)-isomer was added 2 g of pamoic acid in 25 ml of MeOH. The mixture was refluxed for an hour and subsequently colled to room temperature. The precipitate was filtered off yielding 3.0 g of the pamoic acid salt. MP: 264°–266° C., $[\alpha]_D = +13.88°$ C. (c=1, dimethylformamide).

A 2:1 addition compound of the (+)-isomer with L(+)-tartaric acid was prepared in the folowing manner: 4 g of the (+)-isomer as base were dissolved in 100 ml of diethyl ether and extracted into 100 ml of water containing 0.8 g of L(+)-tartaric acid by stirring. The organic phase was separated and discarded. The water-phase was freeze-dried in vacuo (<0.1 mm Hg) for 18 hours leaving 3.8 g of a white powder of the title compound. This addition compound was stable and not hygroscopic.

In a corresponding manner as above via the (+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)benezonitrile, hemi (−)-di-(p-toloyl)tartaric acid salt ($[\alpha]_D = -8.9°$ (c=1, CH_3OH)) which was converted to the corresponding diol base ($[\alpha]_D = +61.1°$ (c=1, CH_3OH)) and finally ringclosure reaction yielded 10 gr of (−)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile. $[\alpha]_D = -12.1°$ (c=1, CH_3OH).

The oxalic acid salt of the (−)-isomer crystallized from acetone. MP: 147°–148° C., $[\alpha]_D = -12.08°$ (c=1, CH_3OH).

EXAMPLE 3

Preparation of citalopram by method (c)

To an ice cooled solution of 28 gr of racemic diol base, II, in 500 ml of dichloromethane were added 32 ml of triethylamine, and 7.5 ml of methansulfonyl chloride in 30 ml of dichloromethane were added dropwise during a half hour. The reaction mixture was washed with 0.1M NaOH solution twice, the organic phase separated, dried ($MgSO_4$) and the solvent evaporated, leaving 21.5 gr of the title (±)-citalopram as a crystalline base. The thus obtained material was dissolved in a mixture of 2-propanol and methanol (2:1) and an equivalent amount of gaseous HBr was introduced. The mixture was left overnight and the precipitated hydrobromide was filtered off. Yield: 26 gr with MP 184°–186° C.

The enantiomers from Example 1 were tested for their ability to block 5-HT reuptake in standard and reliable test method. Results are shown in Table I in comparison with the racemic mixture of citalopram.

5-HTP-POTENTIATION

The test evaluates the ability of the substance to potentiate the effect of 5-HTP, which results in developement of 5-HT syndrome (Christensen, Fjalland, Pedersen, Danneskiold-Samsoe and Svendsen; European J. Pharmacol. 41, 153–162, 1977).

Procedure

Each treatment group consists of 3 mice, and two groups are treated with the highest test dose. A control group only treated with 5-HTP is included and a group treated with citalopram 10 mg/kg and 5-HTP is used as reference for full 5-HT syndrome

The Route of Administration

30 minutes after the administration of the test substance, the other groups are given 5-HTP (100 mg/kg) i.v. (injection time 5–10 sec.). After this 5-HTP dose normal, untreated mice remain unaffected, but if the animals have been pretreated with a substance, which inhibits the uptake of 5-HT or a 5-HT agonist, a 5-HTP syndrome will occur. The symptoms are the same as previously described: (1) excitation, (2) tremor, and (3) abduction of the hind limbs. The animals are observed for 15 minutes and each animal is given one point for each symptom present. Again the result is stated in fractions: 0/9, 1/9, . . . 9/9, where 0, 1, . . . , 9 are the number of points per group after the dose in question. The ED_{50} value is calculated by log-probit analysis.

INHIBITION OF ^{3}H-SEROTONIN UPTAKE IN RAT BRAIN SYNAPTOSOMES

By this method the inhibition by drugs of the uptake of $_3$H-serotonin (^{3}H-5-HT) (10 nM) in rat brain synaptosomes is determined in vitro. Method and results in Hyttel, Psychopharmacology 1978, 60, 13–18; Hyttel, Prog.Neuro-Psychopharmacol. & Biol.Psychait. 1982, 6, 277–295; Hyttel & Larsen, Acta pharmacol. tox. 1985, 56, suppl. 1, 146–153.

Procedure p Male Wistar (Mol:Wist) rats (125–250 g) are sacrified by decapitation and exanguinated. Brain tissue (minus cerebellum) is gently homogenized (glass teflon homogenizer) in 40 vol (w/v) of icecold 0.32M of sucrose containing 1 mM of nialamide. The P_2 fraction (synaptosomal fraction) is obtained by centrifugation (600 g, 10 min and 25000 g, 55 min, 4° C.) and suspended in 800 volumes of a modified Krebs-Ringer-phosphate buffer, pH 7.4.

To 4000 µl of the synaptosomal suspension (5 mg original tissue) on ice are added 100 µl test substance in water. After preincubation at 37° C. for 5 min, 100 µl of ^{3}H-1-NA (final concnetration 10 nM) are added and the samples are incubated for 10 min at 37° C. The incubation is terminated by filtering the samples under vacuum through Whatmam GF/F filters with a wash of 5 ml buffer containing 10 µM of unlabeled 5-HT. The filters are placed in counting vitals and 4 ml of appropriate scintillation fluid (e.g. Picofluor ™15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is determined by liquid scintillation counting. Uptake is obtained by subtracting the nonspecific binding and passive transport measured in the presence of 10 µM citalopram (Lu 10-171-B).

For determination of the inhibition of uptake five concentrations of drugs covering 3 decades are used.

The measured cpm are plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve is drawn. The IC_{50}-value is determined as the concentration, at which the uptake is 50% of the total uptake in control samples minus the nonspecific binding and uptake in the presence of 10 µM of citalopram.

TABLE 1

PHARMACOLOGICAL TEST RESULTS

Compound	5-HTP pot. ED_{50} µmol/kg	5-HT uptake inhibition IC_{50} (nM)
(+)-citalopram	2.0	1.1
(−)-citalopram	120	150
(±)-citalopram	3.3	1.8

(+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile ((+)-citalopram) and the non-toxic acid addition salts thereof may be administered to animals such as dogs, cats, horses, sheeps or the like, including human beings, both orally and parenterally, and may be used for example in the form of tablets, capsles, powders, syrups or in the form of the usual sterial solutions for injection. Results upon administration to human being have been very gratifying.

Most conveniently the compounds of Formula I are administered orally in unit dosage form such as tablets or capsules, each dosage unit containing the free amine or a non-toxic acid addition salt of one of the said compounds in a amount of from about 0.10 to about 100 mg, most preferably, however, from about b 5 to 50 mg, calculated as the free amine, the total daily dosage usually ranging from about 1.0 to about 500 mg. The exact individual dosages as well as daily dosages in a particular case will, of course, be determined according to established medical principles under the direction of a physician.

When preparing tablets, the acitve ingredient is for the most part mixed with ordinary tablet adjuvants such

as corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, or the like.

Typical examples of formulas for composition containing (+)-citalopram in the form of an acid addition salt as the active ingredient, are as follows:

(1) Tablets containing 5 milligrams of (+)-citalopram calculated as the free base:	
Compound 20	5 mg
Lactose	18 mg
Potato starch	27 mg
Saccharose	58 mg
Sorbitol	3 mg
Talcum	5 mg
Gelatine	2 mg
Povidone	1 mg
Magnesium stearate	0.5 mg
(2) Tablets containing 50 milligrams of (+)-citalopram calculated as the free base:	
(+)-citalopram	50 mg
Lactose	16 mg
Potato starch	45 mg
Saccharose	106 mg
Sorbitol	6 mg
Talcum	9 mg
Gelatine	4 mg
Povidone	3 mg
Magnesium stearate	0.6 mg
(3) Syrup containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	500 mg
Tragacanth	7 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Water ad	1 ml
(4) Solution for injection containing per milliliter:	
(+)-citalopram	50 mg
Acetic acid	17.9 mg
Sterile water ad	1 ml
(5) Solution for injection containing per milliliter:	
(+)-citalopram	10 mg
Sorbitol	42.9 mg
Acetic acid	0.63 mg
Sodium hydroxide	22 mg
Sterile water ad	1 ml

Any other pharmaceutical tableting adjuvants may be used provided that they are compatible with the active ingredient, and additional compositions and dosage forms may be similar to those presently used for neuroleptics, analgesics or antidepressants.

Also combinations of (+)-citalopram as well as its non-toxic acid salts with other active ingredients, especially other neuroleptics, thymoleptics, tranquilizers, analgetics or the like, fall within the scope of the present invention.

As previously stated, when isolating the enantiomers of citalopram in the form of an acid addition salt the acid is preferably selected so as to contain an anion which is non-toxic and pharmacologically acceptable, at least in usual therapeutic doses. Representative salts which are included in this preferred group are the hydrochlorides, hydrobromides, sulphates, acetates, phosphates, nitrates, methanesulphonates, ethane-sulphonates, lactates, citrates, tartrates or bitartrates, pamoates and maleates of the amines of Formula I. Other acids are likewise suitable and may be employed if desired. For example: fumaric, benzoic, ascorbic, succinic, salicylic, bismethylenesalicylic, propionic, gluconic, malic, malonic, mandelic, cannamic, citraconic, stearic, palmitic, itaconic, glycolic, benzenesulphonic, and sulphamic acids may be also be employed as acid addition salt-forming acids.

When it is desired to isolate a compound of the invention in the form of the free base, this may be done according to conventional procedure as by dissolving the isolated or unisolated salt in water, treating with a suitable alkaline material, extracting the liberated free base with a suitable organic solvent drying the extract and evaporating to dryness or fractionally distilling to effect isolation of the free basic amine.

The invention also comprises a method for the alleviation, palliation, mitigation or inhibition of the manifestations of certain physiological-psychological abnormalies of animals, especially depressions by administering to a living animal body, including human beings, an adequate quantity of (+)-citalopram or a non-toxic acid addition salt thereof. An adequate quantity would be from about 0.001 mg to about 10 mg per kg of body weight in each unit dosage, and from about 0.003 milligrams to about 7 milligrams/kg of body weight per day.

It is to be understood that the invention is not limited to the exact details of operation or exact compound or compositions shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art.

We claim:

1. A compound selected from substantially pure (+)-1-(3-Dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile and non-toxic acid addition salts thereof.

2. A compound of claim 1 being pamoic acid salt of substantially pure (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

3. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, a compound as defined in claim 1.

4. A pharmaceutical composition in unit dosage form comprising a pharmaceutically acceptable diluent or adjuvant and, as an active ingredient, the compound of claim 2.

5. A pharmaceutical composition in unit dosage form, according to claim 3, wherein the active ingredient is present in an amount from 0.1 to 100 milligram per unit dose.

6. A pharmaceutical composition in unit dosage form, according to claim 4, wherein the active ingredient is present in an amount from 0.1 to 100 miligram per unit dose.

7. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 1 which is effective for said purpose.

8. A method for the alleviation of depression in a living animal body subject thereto which comprises the step of administering to the living animal body an amount of a compound of claim 2 which is effective for said purpose.

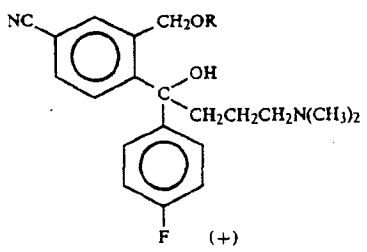
9. Method of claim 10 wherein the compound is administered in the form of a pharmaceutical composition thereof.

10. Method of claim 8 wherein the compound is administered in the form of a pharmaceutical composition thereof.

11. A method for the preparation of a compound as defined in claim 1, which comprises, converting sub-

stantially pure (+)-4-(4-dimethylamino)-1-(4'-fluorophenyl)-1-(hydroxybutyl)-3-(hydroxymethyl)-benzonitrile or a monomester thereof in a stereoselective way to substantially pure (+)-1-(3-dimethylaminopropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile which is isolated as such or as a non-toxic acid addition salt thereof.

12. A compound of the formula



II

wherein R is hydrogen or represents a group completing a labile ester.

* * * * *

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(71) Applicant *(for all designated States except US)*: **H. LUNDBECK A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HUMBLE, Rikke, Eva** [DK/DK]; Æblevej 9, DK-2400 Copenhagen N (DK). **CHRISTENSEN, Troels, Volsgaard** [DK/DK]; Riffelhavevej 15, DK-4300 Holbæk (DK). **ROCK, Michael, Harold** [GB/DK]; Risbjergvej 28, DK-2650 Hvidovre (DK). **NIELSEN, Ole** [DK/DK]; Nystedvej 19, DK-2500 Valby (DK). **PETERSEN, Hans** [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). **DANCER, Robert** [AU/DK]; J.M.Thielesvej 8, st th, DK-1961 Frederiksberg C (DK).

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WO 03/000672 A1

(54) Title: PROCESS FOR THE PREPARATION OF RACEMIC CITALOPRAM AND/OR S- OR R-CITALOPRAM BY SEPARATION OF A MIXTURE OF R- AND S-CITALOPRAM

(57) Abstract: The invention relates to a process for the preparation of racemic citalopram free base or an acid addition salt thereof and/or R- or S-citalopram as the free base or an acid addition salt thereof by separation of a mixture of R- and S-citalopram with more than 50% of one of the enantiomers into a fraction consisting of racemic citalopram and/or a fraction of S-citalopram or R-citalopram characterized in that i) citalopram is precipitated from a solvent as the free base or as an acid addition salt thereof; ii) the precipitate formed is separated from the mother liquor; iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic citalopram, and then optionally converted into an acid addition salt thereof; iib) if the precipitate is not crystalline, steps i) and ii) are optionally repeated until a crystalline precipitate is obtained and the crystalline precipitate is recrystallised one or more times to form racemic citalopram, and then optionally converted into an acid addition salt thereof; iii) the mother liquor is optionally subjected to further purification and S-citalopram or R-citalopram is isolated from the mother liquor and optionally converted into an acid addition salt thereof.

Process for the preparation of racemic citalopram and/or S- or R-citalopram by separation of a mixture of R-and S-citalopram

The invention relates to a process for the preparation of racemic citalopram and/or S- or R-citalopram by separation of a mixture of R- and S-citalopram with more than 50 % of one of the enantiomers into; a fraction of racemic citalopram and/or a fraction of S-citalopram or R-citalopram containing low amounts of the other enantiomer. The invention also relates to a process for the preparation of racemic as well as enantiomerically pure citalopram from the compound R-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile.

Background of the invention

S-citalopram (escitalopram) is the active component of the product citalopram, which is a racemic mixture of the R- and S- enantiomers. The compound is a valuable antidepressant of the selective serotonin reuptake inhibitor (SSRI) type.

Both racemic citalopram and S-citalopram are marketed as antidepressant agents.

It has now surprisingly been found that a mixture of R- and S-citalopram containing more than than 50 % of one or the enantiomers, i.e a non-racemic mixture, may be separated into a fraction of racemic citalopram and a fraction of S- or R-citalopram by precipitation of citalopram as the free base or as an acid addition salt thereof. The surplus of S-citalopram or R-citalopram may be isolated from the mother liquor of the precipitation.

This is an important and very useful process, in particular because it allows the preparation of racemic citalopram and S-citalopram from mixtures of R- and S-citalopram obtained from manufacturing processes which result in mixtures which do not meet the specifications of the marketing approval of neither racemic citalopram nor S-citalopram (in escitalopram, the amount of R-citalopram compared to S-citalopram should be less than 3 %, preferably less).

According to another embodiment of the invention, the mixture of R-and S-citalopram used in step i) contains more than 50 % of S-citalopram, or more preferred more than 90 % of S-citalopram.

In step iii) S-citalopram (or R-citalopram) may be is isolated from the mother liquor by the evaporation of the mother liquor and thereafter optionally the conversion of S-citalopram (or R-citalopram) into an acid addition salt thereof, preferably the oxalate salt.

Alternatively, if the mother liquor obtained from the precipitation is acidic, S-citalopram (or R-citalopram) may be isolated from the mother liquor by basifying the mother liquor, followed by phase separation, or extraction with a solvent and evaporation of the solvent, and thereafter optionally conversion of S-citalopram (or R-citalopram) into an acid addition salt thereof, preferably the oxalate salt.

The mother liquor, extracts thereof, or the phase containing R- or S-citalopram may be subjected to conventional purification processes (such as treatment with active carbon, chromatography, etc.) and/or it may be subjected to further precipitations as in step i)-ii) above before R- or S-citalopram is isolated.

The mixture of R- and S-citalopram with more than 50 % of the S-enantiomer may be prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the S-enantiomer by formation of a labile ester group and thereafter ring closure in a basic environment.

In another embodiment of the invention, the mixture of R- and S-citalopram with more than 50 % of the R-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the R-enantiomer by formation of a labile ester group and thereafter ring closure in a basic environment.

In a further embodiment of the invention, the mixture of R- and S-citalopram with more than 50 % of the S-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the R-enantiomer by ring closure in presence of an acid.

In still a further embodiment of the invention, the mixture of R- and S-citalopram with more than 50 % of the R-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the S-enantiomer by ring closure in presence of an acid.

Preferably, the enantiomeric purity of the starting material R-4-[4 (dimethylamino)-1-(4´fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile is more than 90 %.

The acid used in the acidic ring closure reaction may suitably be a mineral acid such as H_2SO_4 or H_3PO_4, a carboxylic acid, a sulfonic acid or a sulfonic acid derivative.

Whenever used in this document, racemic mixture or racemic citalopram means a 1:1 mixture of R- and S-citalopram. Non-racemic mixtures or non-racemic citalopram means mixtures which do not contain R- and S-citalopram as a 1:1 mixture.

Citalopram means a mixture of R- and S-citalopram. Citalopram enantiomer or isomer means either S- or R-citalopram.

As used in this description, precipitation means forming a precipitate in the form of crystals, an amorphous solid or an oil from a solvent. In the present description, a precipitate means an oil, an amorphous solid or crystals.

As used herein, mother liquor means the solvent remaining after removal or separation from the precipitate.

toluene, benzene and xylene, or mixtures of alcohol and water and mixture of alkanes and alcohols. Thus, both aprotic and protic solvent may be useful.

If necessary crystallisation may be initiated by seeding with racemic crystalline citalopram base.

The precipitation of an acid addition salt of citalopram may be carried out by obtaining or dissolving the non-racemic mixture of R- and S-citalopram in a suitable solvent, if necessary by applying heating, and then adding an acid, either in a solution or as a gas. If crystals are formed, the crystals are separated from the mother liquor, preferably by filtration. The crystals are optionally re-crystallised by dissolving the crystals in a solvent, preferably by heating, and allowing the solution to cool.

If the precipitate formed is not crystalline, but amorphous or an oil, the precipitation process may be repeated until a crystalline product is obtained. The crystals obtained are optionally recrystallised as described above and the racemic citalopram salt may optionally be converted into another salt thereof.

Depending on the ratio of R- and S-citalopram in the starting material, it may be necessary to precipitate (in particular crystallise) the citalopram salt more than once in order to obtain a racemic mixture. The mother liquors from each precipitation or crystallisation may be pooled together and the citalopram enantiomer contained herein may be isolated as described below.

The acid used for precipitation of a citalopram salt is an acid which may precipitate a mixture of R- and S-enantiomer and leave the mother liquor enriched with either the S- or R- enantiomer of citalopram. One such acid is hydrobromic acid.

Suitable solvents for the precipitation and recrystallisation of citalopram salts are protic solvents such as water, alcohols such as methanol and ethanol, ketones such as acetone, and mixtures thereof or aprotic solvent such as acetonitrile or diglyme.

Preparation of Citalopram HBr (racemic) from R-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (R/S ratio: 95,7/4,3) by combination of products obtained from the acidic and the basic ring-closure methods.

Acidic ring closure:

R-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (67.5 g, R/S ratio: 95,7/4,3) was dissolved in toluene (315 mL). At room temperature, a mixture of sulphuric acid (26 g, 96%) and ice (10 g) was added. The mixture was stirred at 78-85 °C for 2 hours. The reaction mixture was cooled and 40 mL water was added. Aqueous ammonia (25% by weight) was added to give a pH 9.5-10.0. The mixture was heated to 55 °C (10 minutes). The phases were separated and the toluene phase was washed three times with water (3 x 65 mL). The toluene was removed at reduced pressure at a maximum of 60 °C to give an oil (oil A). Yield: 63 g (99%).

Basic ring closure of labile ester:

R-4-[4-(dimethylamino)-1-(4´-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile (33.7 g, R/S ratio: 95,7/4,3) was dissolved in acetonitrile (16 g) and toluene (135 mL). 21.4 g Triethylamin was added. A solution of tosylchlorid (19.7 g) and toluene (55 mL) was added to the mixture at a rate so that the temperature was kept bellow 50 °C. The mixture was stirred at 10 °C for 20 minutes. Water (75 mL) was added and the mixture was stirred for 5 minutes. Aqueous ammonia (25% by weight) was added to give a pH of 9.5. The phases were separated and toluene (35 mL) was added to the water phase. This was stirred for 10 minutes at 45 °C. The toluene phases were combined and washed with water (2 x 75 mL). The toluene was removed at reduced pressure at a maximum of 50 °C to give an oil (oil B). Yield: 32.3 g (~100%).

Precipitation of a mixture of oils A and B.

Oil A (57 g) and oil B (28 g) were mixed by dissolving in acetone (310 mL) at room temperature. 35 mL of the solution was removed, HPLC showed an S/R ratio of 49.6/50.4. The mixture was cooled. The pH was 3-4.5. 15 mL of the solution were

Claims:

1. A process for the preparation of racemic citalopram free base or an acid addition salt thereof and/or R- or S-citalopram as the free base or an acid addition salt thereof by separation of a mixture of R- and S-citalopram with more than 50 % of one of the enantiomers into a fraction consisting of racemic citalopram and/or a fraction of S-citalopram or R-citalopram **characterized in that**

i) citalopram is precipitated from a solvent as the free base or as an acid addition salt thereof;

ii) the precipitate formed is separated from the mother liquor;

iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic citalopram, and then optionally converted into an acid addition salt thereof;

iib) if the precipitate is not crystalline, steps i) and ii) are optionally repeated until a crystalline precipitate is obtained and the crystalline precipitate is optionally recrystallised one or more times to form racemic citalopram, and then optionally converted into an acid addition salt thereof;

iii) the mother liquor is optionally subjected to further purification and S-citalopram or R-citalopram is isolated from the mother liquor and optionally converted into an acid addition salt thereof.

2. A process according to claim 1 for the preparation of S-citalopram or R-citalopram **characterized in that**

i) citalopram in the mixture of R- and S-citalopram is precipitated from a solvent as the free base or as an acid addition salt thereof;

ii) the precipitate formed is separated from the mother liquor, and

iii) the mother liquor is optionally subjected to further purification and S-citalopram or R-citalopram is isolated from the mother liquor and optionally converted into an acid addition salt thereof.

3. A process according to claim 1 for the preparation of racemic citalopram **characterized in that**

i) citalopram in the mixture of R- and S-citalopram is precipitated from a solvent as the free base or as an acid addition salt thereof;

ii) the precipitate formed is separated from the mother liquor,

iia) if the precipitate is crystalline it is optionally recrystallised one or more times to form racemic citalopram, and then optionally converted into an acid addition salt thereof;

iib) if the precipitate is not crystalline, steps i) and ii) are repeated until a crystalline precipitate is obtained and the crystalline precipitate is optionally recrystallised one or more times to form racemic citalopram, and optionally converted into an acid addition salt thereof.

4. The method according to claims 1-3 **characterized in that** the acid used for precipitation of citalopram in step i) is an acid which precipitate a mixture of R- and S-enantiomer and leave the mother liquor enriched with either the S- or R- enantiomer of citalopram.

5. The process according to claims 1-4 wherein the salt precipitated in in step i) is the hydrobromide salt, preferably in crystalline form.

6. The process according to claims 1-3 wherein the free base is precipitated in step i).

7. The process according to claims 1-3 **characterised in that** the mixture of R- and S- citalopram with more than 50 % of one of the enantiomers contain more than 50 % of S-citalopram, or more preferred more than 90 % of S-citalopram.

8. The process according to claims 1-2 or 4-7 **characterised in that** S-citalopram is isolated from the mother liquor by evaporation and thereafter optionally converted to an acid addition salt thereof, preferably the oxalate salt.

9. The process according to claims 1-2 or 4-7 **characterised in that** the mother liquor is acidic and S-citalopram is isolated from the mother liquor by basifying the mother liquor, followed by phase separation or extraction with a solvent and evaporation of the solvent, and thereafter optionally conversion of S-citalopram into an acid addition salt thereof, preferably the oxalate salt.

10. The process of claims 1-2 or 4-9 wherein the mother liquor is subjected to one or more further precipitations of citalopram as described under step i) before isolation of the R- or S-citalopram from the mother liquor.

11. The process according to claims 1-9 **characterised in that** a mixture of R- and S-citalopram with more than 50 % of the S-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3 (hydroxymethyl)-benzonitrile with more than 50% of the S-enantiomer by formation of a labile ester group and thereafter ring closure in a basic environment.

12. The process according to claims 1-6 and 8-9 **characterised in that** a mixture of R- and S-citalopram with more than 50 % of the R-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the R-enantiomer by formation of a labile ester group and thereafter ring closure in a basic environment.

13. The process according to claims 1-9 **characterised in that** a mixture of R- and S-citalopram with more than 50 % of the S-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the R-enantiomer by ring closure in presence of an acid.

14. The process according to claims 1-6 and 8-9 **characterised in that** mixture of R- and S-citalopram with more than 50 % of the R-enantiomer is prepared from a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the S-enantiomer by ring closure in presence of an acid.

15. A process for the preparation of a mixture or R- and S citalopram with more than 50 % of the S-enantiomer **characterised in that** a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the R-enantiomer is subjected to ring closure in presence of an acid.

16. A process for the preparation of a mixture or R- and S-citalopram with more than 50 % of the R-enantiomer **characterised in that** a mixture of R- and S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile with more than 50% of the S-enantiomer is subjected to ring closure in presence of an acid.

17. The process according to claims 12, 13 or 15 **characterised in that** the starting material contain more than 90% of R-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile compared to S-4-[4-(dimethylamino)-1-(4′-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-benzonitrile.

18. The process according to claims 13-16 **characterised in that** the acid used in the ring-closure reaction is a mineral acid, a carboxylic acid, a sulfonic acid or sulfonic acid derivative.

19. The process according to claim 18 **characterised in that** the acid is H_2SO_4 or H_3PO_4.

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(71) Applicant *(for all designated States except US)*: **H. LUNDBECK A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CHRISTENSEN, Troels, Volsgaard** [DK/DK]; Riffelhavevej 15, DK-4300 Holbæk (DK). **LILJEGREN, Ken** [DK/DK]; Langkær Vænge 10, DK-3500 Værløse (DK). **ELEMA, Michiel, Onne** [NL/DK]; Victor Bendix Gade 11, 2 th, DK-2100 København Ø (DK). **ANDRESEN, Lene** [DK/DK]; Rødovrevej 220C, 1 tv, DK-2610 Rødovre (DK). **MAHASHABDE, Shashank** [US/US]; 13 Village Road, Kendall Park, NJ 08825 (US). **ASSENZA, Sebastian, P.** [US/US]; 15 Truxton Lane, Fort Salonga, NY 11768 (US).

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(54) Title: CRYSTALLINE COMPOSITION CONTAINING ESCITALOPRAM

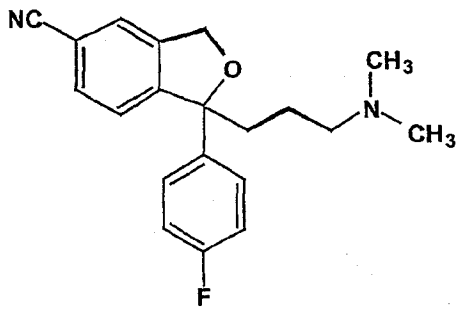
(57) Abstract: Crystalline particles of escitalopram oxalate with a particle size of at least 40µm is disclosed. Method for the manufacture of said crystalline particles and pharmaceutical compositions comprising said crystalline particles are also disclosed.

Crystalline composition containing Escitalopram

The present invention relates to crystalline preparations of the oxalate salt of the compound escitalopram (INN-name), which is the S-enantiomer of the well-known antidepressant drug citalopram, i.e. (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile oxalate.

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.

Escitalopram, the pharmaceutical activity thereof and crystalline escitalopram oxalate are disclosed in US Patent No 4,943,590. Methods for preparation of pharmaceutical preparations of escitalopram are outlined.

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

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 hydrobromide during tabletting, it was considered necessary to make a granulate of citalopram hydrobromide 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.

We have found that escitalopram has significantly different solubility and salt formation properties from the citalopram racemate. For example, the only pharmaceutically crystalline salt known so far is the oxalate, whereas the citalopram racemate forms crystalline hydrobromide and hydrochloride salts as well.

The escitalopram oxalate product prepared by crystallisation from acetone as outlined in US Patent No 4,943,590 has, as the citalopram hydrobromide product described above, a very small particle size around 2-20 μm resulting in similarly poor flow properties.

In view of the fact that direct compression is much simpler and cheaper than the processes involving granulation there is a desire for larger crystals of escitalopram or pharmaceutical acceptable addition salts thereof.

Extensive laboratory and full-scale research has resulted in a new and inventive crystallisation process producing larger crystalline particles of escitalopram oxalate, i.e. particles of a size comparable to the size of the filler. Said particles are useful for the manufacture of directly compressed tablets. Accurate dosing in capsules may also be with such large particles.

Objects of the Invention

It is the object of the present invention to provide large crystalline particles of escitalopram oxalate suitable for use in direct compression.

A second object of the invention is to provide a method for manufacture of large crystalline particles of escitalopram oxalate.

A third object of the invention is to provide a novel pharmaceutical unit dosage form containing large crystalline particles of escitalopram oxalate, wherein said unit dosage form may be a tablet, which preferably may be prepared by direct compression, or a capsule.

Summary of the Invention

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

Crystalline particles of escitalopram oxalate with a median particle size of at least 40 µm and suitable for use in a solid unit dosage form.

A method for the manufacture of crystalline particles of escitalopram oxalate having a median particle size of at least 40 µm and suitable for use in a solid unit dosage form wherein said method comprises that a solution of escitalopram oxalate in a suitable solvent system at a first temperature is gradually cooled down to a second temperature maintaining a controlled cooling profile and seeding the crystallisation batch by addition of crystals of escitalopram oxalate at least once during the cooling and followed by a holding time at said second temperature whereupon said crystals are isolated by conventional solid/liquid separation techniques.

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

The direct compression of escitalopram, 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, "escitalopram oxalate" means any addition salt consisting of escitalopram, oxalic acid and optionally water. Examples of such salts are the hydrogen oxalate salt of escitalopram, i.e. the salt consisting of one molecule of escitalopram per molecule of oxalic acid, as well as the oxalate salt of escitalopram, i.e. the salt consisting of two molecules of escitalopram per molecule of oxalic acid.

As used herein, "crystalline particles" means any combination of single crystals, aggregates and agglomerates.

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 cumulative volume size 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.

As used herein, "cooling profile" means the temperature of the crystallisation batch as a function of time.

As used herein, "cooling rate" means the decrease in temperature per time unit.

Thus in one embodiment of the present invention the crystalline particles of escitalopram oxalate have a median particle size of at least 40 μm, preferably in the range of 50 – 200 μm.

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

In another embodiment of the present invention crystalline particles of escitalopram oxalate having a median particle size of at least 40 μm, preferably in the range of 50 – 200 μm, and suitable for use in a solid unit dosage form are crystallised from a solution of escitalopram oxalate in a suitable solvent system. Said solvent system may comprise one or more alcohols and optionally water, preferably the solvent system is ethanol. Escitalopram oxalate 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 70 °C and the refluxing temperature, suitably the escitalopram oxalate is dissolved at the refluxing temperature. The amounts of pharmaceutically acceptable salt of escitalopram and solvent used are preferably corresponding to a solvent:solute weight ratio in the range of 0.05:1 to 0.6:1, more preferred 0.1:1 to 0.5:1 and most preferred 0.2:1 to 0.4:1. The solution of escitalopram oxalate is gradually cooled down to the temperature, at which the crystals will be isolated from the mother liquor, in the range of 0-20 °C, preferably 0-15 °C, and more preferred 7-15 °C maintaining a controlled cooling profile so that the cooling rate in an initial cooling period does not exceed 0.6 °C/min, and preferably the cooling rate is kept within the range of 0.2 – 0.4 °C/min, and said initial cooling period extends until the temperature of the crystallisation batch is below 60 °C, preferably below 50 °C and more preferred below 40 °C, suitably the cooling rate may be kept in this range for the entire cooling. The crystallisation batch is seeded by addition of crystals of escitalopram oxalate at least once during the cooling time in order to avoid excessive supersaturation with respect to escitalopram oxalate and resulting spontaneous crystallisation into small crystalline particles. The seeding is preferably repeated in order to ensure constant presence of crystalline escitalopram oxalate during the cooling, suitably the crystallisation batch is seeded semicontinuosly until crystallisation has started. The crystallisation batch is kept at said second temperature for a holding time for crystal growth for at least 1 hour, preferably in the range of 4 to 24 hours and more preferred 6 to 12 hours. After said holding time, the crystalline particles of escitalopram are

isolated from the mother liquor using conventional separation techniques, e.g. filtration.

In one embodiment of the invention, the present invention relates to a tablet prepared from a mixture of large crystalline particles of escitalopram oxalate with a median particle size of at least 40 µm, preferably in the range of 50 – 200 µm and pharmaceutically acceptable excipients. Preferably the tablet is prepared by direct compression.

In another embodiment, the present invention relates to a capsule prepared by filling a mixture of large crystalline particles of escitalopram oxalate with a median particle size of at least 40 µm, preferably in the range of 50 – 200 µm and pharmaceutically acceptable excipients in a hard gelatine capsule.

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 1-60% w/w active ingredient calculated as escitalopram base, preferably 4-40% w/w active ingredient calculated as escitalopram base, and more preferred 6-10% w/w active ingredient calculated as escitalopram base. Suitably, the solid unit dosage form of the invention contains 8% w/w active ingredient calculated as escitalopram base.

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 selected from the group comprising metallic stearates (magnesium, calcium, sodium), stearic acid, wax, hydrogenated vegetable oil, talc and colloidal silica.

Preferably the lubricant is one or more selected from the group comprising talc, magnesium stearate or calcium stearate. Suitably the lubricant is a combination of talc and magnesium stearate. The weight percent of magnesium stearate in the solid unit dosage form is preferably in the range of 0.4% to 2%, and more preferred in the range of 0.7% to 1.4%.

Disintegrants include sodium starch glycolate, croscarmellose, crospovidone, low substituted hydroxypropylcellulose, modified cornstarch, pregelatizined starch and natural starch. Suitably the disintegrant is crosscarmellose such Ac-Di-Sol manufactured by FMC.

Optionally the solid, pharmaceutical unit dosage form of the invention may be coated. Suitably the coating is a film coating based on conventional coating mixtures such as Opadry OY-S-28849, white manufactured by Colorcon.

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 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.

Tablet core		
Escitalopram oxalate	2554 g	(10.2 % w/w)
Talc	1400 g	(5.6 % w/w)
ProSolv SMCC90	19896 g	(79.6 % w/w)
Ac-Di-Sol	900 g	(3.6 %
Magnesium stearate	250 g	(1.0 % w/w)
Film coating		
Opadry OY-S-28849, white	625 g	(2.5 % w/w of core weight)

Crystalline particles of escitalopram oxalate from example 1 and talc were sieved through 710 µm screen and blended at 6 rpm for 15 min in a 100 litre Bohle PTM 200 mixer. ProSolv SMCC90 and Ac-Di-Sol were added and blending continued for 15 min. Magnesium stearate was sieved through 710 µm screen and added and blending continued for 3 min.

25 kg of the resulting mixture was tabletted (125.000 tablets/hour) on a Korsch PH 230 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. The tablets produced had satisfactory technical properties.

pueden realizar en los ensayos de cesión *in vitro* (incorporación de tensioa
con principios activos muy poco solubles, distintos fluidos acuosos...) y en al
casos se puede acabar concluyendo que, al no existir correlación en esas for
ciones, no tiene sentido realizar ensayos de cesión *in vitro* como sucede con
nos productos muy lipófilos como vitaminas liposolubles o algunos ésteres d
tromicina.

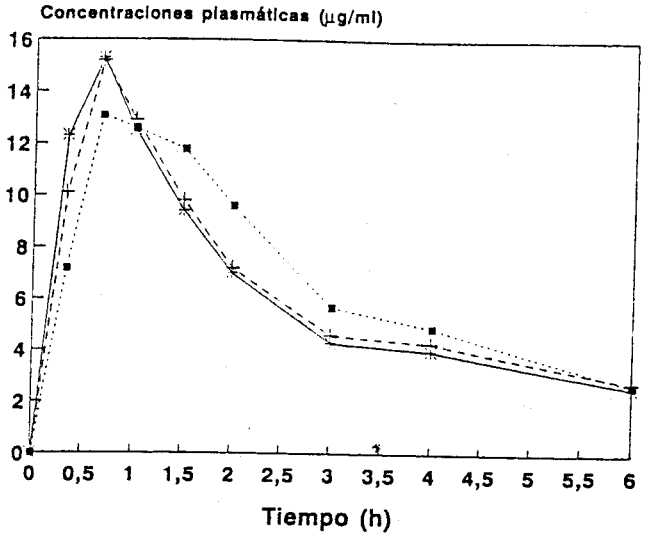


FIGURA 1.8. Concentraciones plasmáticas de paracetamol obtenidas después de la administrac
oral de tres formulaciones de paracetamol. *: granulado de paracetamol; +: microcápsulas
paracetamol; ■: microcápsulas de paracetamol recubiertas con polímero acrílico.

1.4. Consideraciones fisicoquímicas

En este epígrafe se incluyen los estudios destinados a conocer en profundidad
sustancia activa, para obtener el máximo de datos de interés galénico y conocer la
propiedades fisicoquímicas de la sustancia activa pura y en mezcla con determinado
disolventes, excipientes y materiales de acondicionamiento. Algunos de estos estu
dios se llevan a cabo en condiciones extremas de temperatura, luz , humedad y ox
geno para acelerar y así poder detectar posibles reacciones entre los componentes.

1.4.1. Descripción del estado físico

El primer paso en el conocimiento de una sustanci dría ser la descripción
de su estado físico. La mayoría de los fármacos utilizados en la actualidad son sóli-

dos a las condiciones de temperatura y presión ambientales. Los pri
al estado líquido son menos habituales y aún son menos frecuentes
activas gaseosas.

Entre los escasos fármacos de naturaleza líquida que se emplea
dad se encuentran el nitrato de amilo (vasodilatador), el clofibrato
démico), el dimecaprol (antídoto para el envenenamiento producid
oro o mercurio), la nitroglicerina (antianginoso), la parametadiona
vante) y el ácido undecilénico (antifúngico), entre otros.

Los principios activos líquidos entrañan algunos problemas adi
do se aborda su preformulación. Muchos de ellos son sustancias
consecuencia, deben de ser manejados en recipientes herméticam
para aislarlos de la atmósfera y así evitar pérdidas. El nitrato de an
plo, es un líquido amarillento volátil e inflamable incluso a bajas
Se formula al estado líquido y se dosifica en ampollas de vidrio sel
tienen una gasa. En el momento de la administración se rompe l
los dedos, el líquido humecta la gasa y se producen los vapores
paciente.

Este tipo de fármacos líquidos no se puede formular en forma
dos, pero la nitroglicerina constituye una excepción. Se formula en
para su administración sublingual. Como tiene tendencia a liberar
mido durante el período de almacenamiento, es importante que los
se acondicionen en recipientes de vidrio, si no van provistos de un
que les aisle.

1.4.2. Microscopia

El exámen microscópico de la materia prima constituye una
tante dentro de la fase de preformulación. Esta técnica suministr
sobre la forma de las partículas: si son aciculares, laminares, de as
etc. Asimismo se puede determinar si son de aspecto cristalino
tamaño de partícula es un parámetro que también se puede de
microscopia, e incluso puede proporcionar información de si ha h
caciones relativas al tamaño medio o a la forma a causa a la manip
materia prima en alguna fase de los estudios de preformulación, o
tar con las microfotografías las posibles diferencias entre las pa
lote a otro.

1.4.3. Tamaño de partícula

La disolución, la reactividad química y la fluidez de una sustanc
homogeneidad de la formulación que la contiene, dependen del tar

morfología de la superficie de las partículas que constituyen dicha sustancia ac
va. Por ello, tiene gran interés en la fase de preformulación el análisis granulom
trico, que proporciona información sobre el tamaño medio de las partículas,
homogeneidad y la forma de las mismas.

Las técnicas de análisis granulométrico habitualmente utilizadas son la micro
copia óptica y la tamización analítica. Y para conocer directamente la superfic
específica se emplea la técnica de adsorción de gases.

Para utilizar la microscopia óptica es necesario acondicionar previamente
muestra. Se prepara una suspensión de las partículas en un líquido de índice d
refracción adecuado y en el que sean prácticamente insolubles. Se deposita un
gota de la suspensión entre un portaobjetos y un cubreobjetos y la muestra a
preparada se observa al microscopio. Para medir las partículas correctamente e
microscopio debe llevar acoplado un ocular Watson. El número de partículas qu
hay que medir será como mínimo 100. Las partículas, según su tamaño, se agru
pan en intervalos cuya amplitud seguirá una progresión previamente fijada
constante.

Cada vez tiene más auge la utilización de técnicas de difracción de rayo láse
y de espectroscopia de correlación fotónica.

1.4.4. Cristalinidad y polimorfismo

En la figura 1.9 se recogen algunas de las diferentes posibilidades en las que se
puede presentar una sustancia al estado sólido. El hábito cristalino y la estructura
interna de una sustancia activa puede afectar a alguna de sus características tales
como fluidez y estabilidad química. Hábito cristalino es la descripción del aspecto
externo de los cristales, mientras que la estructura interna es la disposición de los
elementos dentro del sólido. Una sustancia con una misma estructura cristalina
interna puede presentarse con diferentes hábitos cristalinos en función de las
condiciones en que ha cristalizado.

Por otro lado, se ha de diferenciar en la estructura interna de una sustancia al
estado sólido las dos posibilidades de sustancia cristalina y amorfa. En la sustan-
cia cristalina se repite a lo largo de las tres dimensiones del espacio la disposición
de los átomos, moléculas o iones. En la sustancia amorfa no aparece esta ordena-
ción. En ocasiones se puede conseguir que una sustancia solidifique al estado amor-
fo a partir de una disolución mediante precipitación o enfriamiento rápidos o por
un proceso de liofilización.

Las sustancias amorfas son inestables y tienden a transformarse en cristalinas
en un período de tiempo más o menos prolongado. Dado que sus características
de fusión, disolución, etc., son diferentes (hay que aportar más energía para fun-
dir o disolver una sustancia cristalina que una amorfa), en el período de reposición
de las formas farmacéuticas se podría producir este cambio, con lo que se verían
afectadas sus características macroscópicas (disoluciones que precipitan, creci-

miento cristalino en suspensiones y supositorios), así como su proc
ción, es decir, su biodisponibilidad. Esto constituye el mayor inconven
una sustancia amorfa en una forma de dosificación.

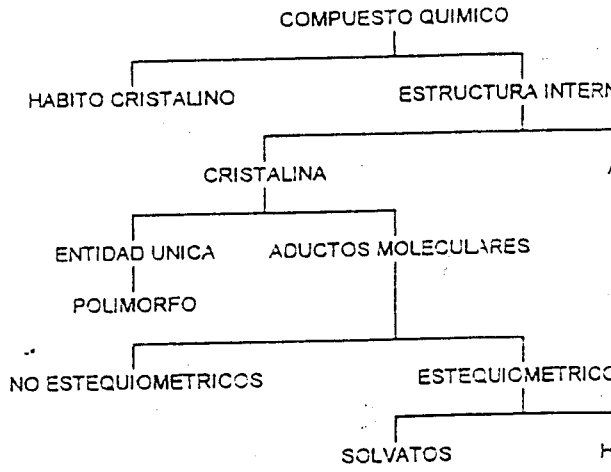


FIGURA 1.9. Diferentes posibilidades en que puede aparecer un compuesto químico

Un compuesto cristalino puede cristalizar con una determinad
disolvente. Si el disolvente de cristalización no está en proporcione
tricas con la sustancia activa, esta posibilidad al estado sólido se debe
las dificultades que entraña su reproductibilidad. Si el disolvente de
está en proporciones estequiométricas, origina los solvatos, de los
incluirán en el estudio de preformulación los hidratos.

La identificación de los hidratos es importante, porque sus parám
bilidad pueden ser significativamente inferiores a los de las formas a
podría redundar en la velocidad y cantidad de fármaco absorbido, al
to en una forma farmacéutica.

En múltiples ocasiones cuando se inicia la preformulación no s
cadas todas las posibles formas al estado sólido del principio activo
aparición de diversos polimorfos. "Polimorfismo" es un término téc
liza en Biología y en Cristalografía para describir el hecho de que
natural pueda tener lugar de dos o más formas diferentes.

En Cristalografía el polimorfismo se refiere a materiales crista
o sintéticos. Si una sustancia se presenta en dos formas cristalinas,

tura dada, sólo una es estable y la otra es la forma inestable o metastable. A veces hay más de dos formas cristalinas, como es el caso del fenobarbital, del que se han identificado hasta once formas diferentes; para su denominación se comienza adjudicándole el término I al polimorfo de mayor punto de fusión, y II, III, etc., a los que presentan puntos de fusión en orden decreciente.

La importancia que puede tener el que un fármaco posea dos o más formas cristalinas se debe a que, al ser entidades químicamente idénticas, pero físicamente diferentes, las características que derivan de su estructura al estado sólido también difieren. Así, presentarán no sólo diferente punto de fusión, sino que también pueden tener diferente densidad, capacidad para fluir, compresibilidad, calores de fusión y disolución, solubilidad, etc. Estas diferencias pueden originar dificultades en los procesos tecnológicos de elaboración de las formas farmacéuticas cuando se pase de utilizar un polimorfo a otro. Asimismo, si se trabaja con la forma metastable es probable que durante el almacenamiento de algunas formas farmacéuticas se produzca la transición hacia la más estable, originando, como en el caso de la transición amorfo/cristalino, dificultad en redispersión cuando se trata de suspensiones, crecimiento cristalino, etc.

Por lo anteriormente expuesto, el fenómeno del polimorfismo puede provocar alteraciones relativas a la biodisponibilidad del fármaco en función del polimorfo que, incluido en la forma farmacéutica, se administra al organismo. La utilización del polimorfo que tenga mayor solubilidad puede proporcionar niveles sanguíneos suficientes para obtener una acción terapéutica, mientrás que la forma estable al disolverse más lentamente y en menor proporción puede dar lugar a concentraciones en sangre que resulten insuficientes para lograr una acción terapéutica. Este hecho se ha puesto de manifiesto en diferentes ocasiones. Así, del palmitato de cloranfenicol se conocen dos polimorfos denominados A y B (según la nomenclatura indicada anteriormente les correspondería la denominación I y II). El polimorfo A, más estable y de mayor punto de fusión, presenta menor biodisponibilidad que el polimorfo B, inestable, de menor punto de fusión y mayor solubilidad.

Las fases que hay que seguir para investigar el polimorfismo en la nueva molécula serían:

— Recristalización a partir de los disolventes habitualmente empleados en las últimas etapas de la síntesis y en los procesos tecnológicos de elaboración de formas farmacéuticas.
— Identificación de los cristales obtenidos mediante difracción de rayos X y al menos otra técnica de evaluación del polimorfismo como espectroscopia de infrarrojos, calorimetría diferencial de barrido, microscopia, etc.
— Si se confirma la existencia de polimorfos, se cuantifican las características fisicoquímicas que pueden afectar a la biodisponibilidad, estabilidad y reproductibilidad de los procesos de fabricación. Así se determinaría el perfil de solubilidad, estabilidad, morfología cristalina, comportam(o calorimétrico y perfil de humedades de equilibrio.

— Si los resultados indican que las propiedades físicas de l hallados pueden afectar a la calidad y/o la biodisponibilid a partir de la forma de dosificación, es necesario desarrol reproductible para sintetizar siempre el polimorfo deseado de evitar en la síntesis la mezcla de polimorfos, es necesa control cuantitativo, previamente validado, para asegurar de polimorfos.

Actualmente, en los laboratorios farmacéuticos, las técnicas a utilizan para caracterizar el estado sólido y detectar así la posible pr morfos, amorfos, hidratos, etc., son las que se indican a continuaci

Las técnicas de microscopia óptica y electrónica de barrido sir guir la forma y el aspecto de las partículas; luego proporcionarán inf el hábito cristalino y detectarán las sustancias amorfas. La microsc ca de barrido no es una técnica rutinaria dentro del laboratorio fa la dificultad que entraña la preparación de la muestra y lo costos manejo y mantenimiento de los equipos.

Existen también distintas técnicas de análisis térmico:

— La microscopia de platina caliente permite detectar visual bios que sufre una muestra durante el aporte de calor. Entr nos se puede determinar cualitativamente la pérdida de cristalización, las transformaciones cristalinas, los procesos d talización, la sublimación y recristalización, la descomposic
— La calorimetría diferencial de barrido (DSC) cuantifica l sufre una muestra durante su calentamiento, indicando si el p térmico (pérdida de disolvente, fusión, etc.) o exotérmico (descomposición, etc.). Asimismo, permite detectar la prese zas, dado que uno de los datos que se pueden calcular por c rencial de barrido es la pureza de la sustancia analizada.
— La termogravimetría mide los cambios de peso que experi tra al aumentar la temperatura o a lo largo del tiempo a u determinada.

En la figura 1.10 se recogen las curvas de DSC correspondie morfos y un hidrato de la prednisolona.

La técnica de difracción de rayos X en polvo proporciona un característico de la sustancia activa e indica si es amorfo o crista técnica no destructiva, permite su utilización en la caracterización tancias cuyo tamaño de lote es muy reducido. Cuando existen d posible recr( )lización a partir de un amorfo, o de transformación fo en otro, esta técnica proporciona resultados concluyentes, pu

que el espectro de rayos X es como la huella digital de cualquier compuesto a
do sólido.

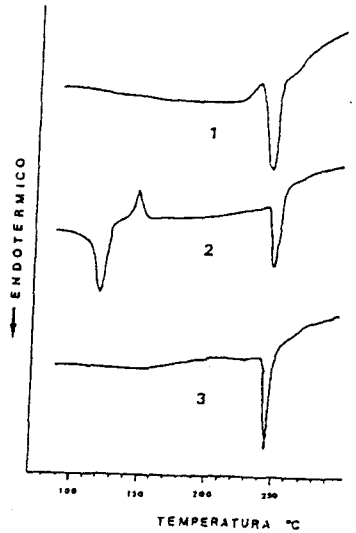


FIGURA 1.10. Curvas de DSC de prednisolona: (1) forma I, anhidra; (2) hidrato de la forma I; forma II.

En la figura 1.10 se recogen los espectros de difracción de rayos X de las dife
rentes formas de ampicilina según la Farmacopea de los Estados Unidos de 199
(USP 23).

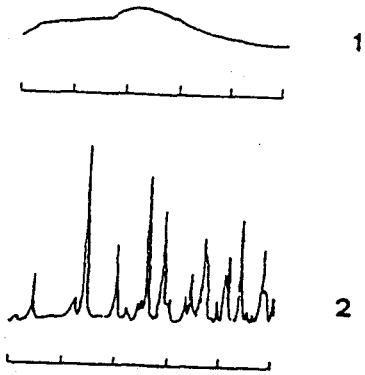


FIGURA 1.11. Espectros de difracción de rayos X de cuatro formas sólidas de ampicilina (USP 23): (1) ampicilina amorfa (anhidra), (2) ampicilina trih o.

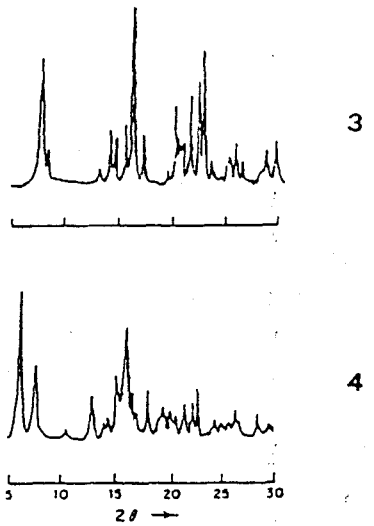


FIGURA 1.11. (continuación) (3) polimorfo 1 de ampicilina anhidra, (4) polimorfo anhidra.

1.4.5. *Punto de fusión*

La determinación del punto de fusión de un principio activo pue
lizando fundamentalmente tres técnicas:

— Método del capilar.
— Microscopia de platina caliente.
— Calorimetría diferencial de barrido.

El método del capilar consiste en la observación directa, o bajo lu
tra introducida en un capilar, el cual se encuentra en contacto con u
lica con calentamiento programado. Así se obtiene información sob
de fusión, pero resulta difícil determinar de forma exacta el punto
La microscopia de platina caliente permite la observación micr
partículas, tal y como se indicó en el apartado de polimorfismo. El
equipado con una platina que se calienta a una velocidad controla
registrar el inicio de la fusión, la temperatura a la que funde la mit
tra y la fusión total.
La calorimetría diferencial de barrido proporciona, no sólo el p
exacto, sino también el calor de fusión. La presencia de impurezas se d
método de an s térmico como se ha comentado anteriormente. E
se recogen las c vas de DSC del ácido benzoico con diferentes grados

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REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE JULIO - - - -

DEL AÑO DOS MIL DOS (2002). ----------

ACTO: ----------

1.- PODER ESPECIAL.----------

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-8 - - - - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No. 79.152.473 de Usaquén - Bogotá.---------

Como Notario Veintiséis del Circulo de Bogotá, hago constar que esta copia es fiel y con original que se ha presentado para su autenticación. Bogotá, D.C. Colombia

22 FEB. 2006

GONZALO L. DELGADO CASTRO
NOTARIO 26 ENCARGADO

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL, DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA, ANTE MI, DIANA BEATRIZ LOPEZ, - - - - - -

NOTARIA TREINTA Y TRES (33) - - - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE SE CONSIGNA EN LOS SIGUIENTES TERMINOS:----------

COMPARECIO: JUAN MARIA RENDON, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 17.125.100 - - - - -

Expedida en Bogotá - - - - - - -

Y manifestó:----------

PRIMERO: Que obra en su carácter de Representante Legal de en nombre y representación de LAFRANCOL S.A, sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio

promueva Lafrancol S.A., o se promuevan contra esta y.---------

c.- Para que en todos los asuntos arriba determinados, tanto en los términos señalados por los artículos 42 y complementarios de la decisión 486 de la Comunidad Andina como del artículo 70 del C.P.C. pueda sustituir este mandato, transigir, conciliar,admitir los hechos del proceso, desistir, cancelar, recibir, renunciar y ratificar los actos de agentes oficiosos y ceder a título gratuito y/o oneroso, licenciar, inscribir contratos de cesión y de licencia, inscripción de prendas, levantamiento de prendas, inscribir derechos de retención y en general todos los asuntos que se deban tramitar ante la Superintendencia de Industria y Comercio.----------

Manifestamos que de la veracidad de las declaraciones del contenido y autenticidad de los documentos anexos en éste instrumento público sólo respondemos los comparecientes.-

HASTA AQUI LA MINUTA PRESENTADA

OTORGAMIENTO Y AUTORIZACION: Leído el presente instrumento Público por los comparecientes y advertidos de la formalidad de su contenido, dentro del término legal, lo hallaron conforme con sus intenciones y lo aprobaron en todas sus partes y firmaron junto con la Suscrita Notaria quien da fe y lo autoriza. -----

Se utilizaron las hojas de papel Notarial Números

01

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20071128 Hora Certificado 11:54:17

Operacion : 02C161128038 PAGINA No. 1

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null

CERTIFICA:

NOMBRE:LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL :---K 1 46 84
DIRECCION NOTIFICACION JUDICIAL:---K 1 46 84
CIUDAD:CALI
MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958
DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net
AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO. INS LIBRO
E.P. 1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	19467
E.P. 2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	20089
E.P. 1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	24528
E.P. 1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	26360
E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963	26717
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964	

*** CONTINUA ***

ESCRITURA NUMERO CUATRO MIL QUINIENTOS - TREINTA Y NUEVE (No.4.539) ---------------

En la ciudad de Cali, Capital del Departamento del Valle del Cauca, República de Colombia, a los VEINTITRES (23) días - del mes de OCTUBRE del año DOS MIL UNO -- (2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario T E R C E R O (3o.) del Círculo de Cali, -

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali, identificado con la cédula de ciudadanía número 14.949.561 de Cali, y dijo: ----

PRIMERO.- Que obra en su carácter de Representante Legal de en nombre y representación de TECNOQUIMICAS S.A., sociedad comercial organizada y existente conforme a las leyes colombianas, con domicilio y sede principal en Cali constituida mediante escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de junio de 1957, reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali ---

SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial pero amplio y suficiente a JOSE LUIS REYES VILLAMIZAR, mayor de edad, vecino de Bogotá, identificado con C.C. # 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P 44655 del C.S.de la J., domiciliado en Bogotá, D.C., República de Colombia con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección de nuestra propiedad industrial y contra la competencia desleal, a cuyo efecto lo autorizo, para que nos represente ante cualesquiera entidad o persona, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, en todo lo concerniente a los siguientes asuntos: a) Obtención, formulación de observaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos; b) Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales,

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20071226 Hora Certificado 13:56:33

Operacion : 02NBM1226042 PAGINA No. 1

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CERTIFICA:

NOMBRE:TECNOQUIMICAS S A
DOMICILIO: CALI VALLE
DIRECCION COMERCIAL :---C 23 7 39
DIRECCION NOTIFICACION JUDICIAL:---C 23 7 39
CIUDAD:CALI
MATRICULA MERCANTIL NRO. 7049-4 FECHA MATRICULA : 01 DE JULIO DE 1957
AFILIADO

CERTIFICA:

NIT : 890300466-5

CERTIFICA:

QUE POR ESCRITURA NRO. 2670 DEL 12 DE JUNIO DE 1957 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 01 DE JULIO DE 1957 BAJO EL NRO. 16627 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA COMPANIAS TECNOQUIMICAS LIMITADA

CERTIFICA:

QUE POR ESCRITURA NRO. 8438 DEL 30 DE DICIEMBRE DE 1970 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 07 DE ENERO DE 1971 BAJO EL NRO. 42260 DEL LIBRO IX ,LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD LIMITADA EN SOCIEDAD EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) .

CERTIFICA:

QUE POR ESCRITURA NRO. 2139 DEL 21 DE ABRIL DE 1972 NOTARIA SEGUNDA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 26 DE ABRIL DE 1972 BAJO EL NRO. 794 DEL LIBRO IX , LA SOCIEDAD CAMBIO SU NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) . POR EL DE TECNOQUIMICAS LIMITADA & CIA S.C. A. .

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E.P. 8853	30/12/1963	NOTARIA PRIMERA DE CALI		23/01/1964
27107				
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI		10/02/1964
27181				
E.P. 2743	29/04/1964	NOTARIA PRIMERA DE CALI		06/05/1964
27681				
E.P. 2744	29/04/1964	NOTARIA PRIMERA DE CALI		06/05/1964
27682				
E.P. 7057	21/10/1964	NOTARIA PRIMERA DE CALI		22/10/1964
28591				
E.P. 1693	26/04/1965	NOTARIA PRIMERA DE CALI		28/04/1965
29569				
E.P. 1799	10/05/1966	NOTARIA PRIMERA DE CALI		11/05/1966
31623				
E.P. 2498	18/11/1966	NOTARIA CUARTA DE CALI		25/11/1966
32757				
E.P. 2792	27/12/1966	NOTARIA CUARTA DE CALI		05/01/1967
33009				
E.P. 2209	25/09/1967	NOTARIA CUARTA DE CALI		04/10/1967
34591				
E.P. 6933	20/12/1967	NOTARIA SEGUNDA DE CALI		28/12/1967
35082				
E.P. 6363	14/11/1968	NOTARIA SEGUNDA DE CALI		26/11/1968
37141				
E.P. 7711	31/12/1968	NOTARIA SEGUNDA DE CALI		04/02/1969
37615				
E.P. 5597	30/09/1969	NOTARIA SEGUNDA DE CALI		18/10/1969
39341				
E.P. 5211	27/08/1970	NOTARIA SEGUNDA DE CALI		04/09/1970
41379				
E.P. 6576	07/10/1971	NOTARIA SEGUNDA DE CALI		14/10/1971
44154				
E.P. 7286	08/11/1971	NOTARIA SEGUNDA DE CALI		10/11/1971
44367				
E.P. 8042	03/12/1971	NOTARIA SEGUNDA DE CALI		21/12/1971
44716				
E.P. 6209	05/10/1973	NOTARIA SEGUNDA DE CALI		15/10/1973
5505 IX				
E.P. 8741	31/12/1973	NOTARIA SEGUNDA DE CALI		08/03/1974
7636 IX				
E.P. 9270	31/12/1974	NOTARIA SEGUNDA DE CALI		31/01/1975
11772 IX				
E.P. 9504	31/12/1974	NOTARIA SEGUNDA DE CALI		04/04/1975
12441 IX				
E.P. 7566	05/12/1975	NOTARIA SEGUNDA DE CALI		09/01/1976
15581 IX				
E.P. 2671	09/05/1980	NOTARIA SEGUNDA DE CALI		22/10/1980
41529 IX				

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COMERCIO EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS, ALIMENTOS NATURALES Y/O PROCESADOS, PRODUCTOS DE CONSUMO POPULAR, SERVICIOS EN GENERAL O LA EXPLOTACION DE ESTABLECIMIENTOS DE COMERCIO DEDICADOS A DICHO GIRO. C) ADQUIRIR ACCIONES, CUOTAS SOCIALES, BONOS CEDULAS, TITULOS U OTROS VALORES EN COMPANIAS DE CUALQUIER NATURALEZA O TIPO LEGAL, DEDICADAS A LA EXPLOTACION DE CUALQUIER ACTIVIDAD ECONOMICA LICITA Y ENAJENARLAS.D) LA EXPLOTACION DEL NEGOCIO DE LA PUBLICIDAD Y EL ESTABLECIMIENTO DE OFICINAS DEDICADAS A ESTE NEGOCIO O A LA CREACION DE ORGANOS DE PUBLICIDAD HABLADOS O ESCRITOS. E) GARANTIZAR LAS OBLIGACIONES PROPIAS DE LOS ACCIONISTAS O DE TERCEROS. F) LA ADQUISICION DE BIENES MUEBLES, INMUEBLES Y DE TODA CLASE DE EQUIPO Y MAQUINARIA PARA SU ARRENDAMIENTO O PARA LA COMERCIALIZACION DE ELLOS. EN DESARROLLO DEL OBJETO SOCIAL PODRA OBTENER PRIVILEGIOS INDUSTRIALES, CONCESIONES, PATENTES DE INVENCION, DE MEJORAS O PROCEDIMIENTOS, MARCAS DE FABRICA O DE COMERCIO, YA SEA EN NOMBRE PROPIO O DE TERCEROS, OTORGAR A TERCEROS, DENTRO O FUERA DEL PAIS CONCESIONES O USOS DE EXPLOTACION SOBRE ESTOS DERECHOS, EJECUTAR TODA CLASE DE CONTRATOS DE COMPRAVENTA, DISTRIBUCION DE MATERIAS PRIMAS, DE PRODUCTOS SEMIELABORADOS O ELABORADOS EN EL MERCADO INTERNO O EN EL EXTERIOR Y EN GENERAL, LA CELEBRACION DE TODO ACTO O CONTRATO SOBRE BIENES MUEBLES O INMUEBLES DE COMERCIO, INDUSTRIALES O DE OTRA INDOLE QUE SE REFIERAN DIRECTAMENTE A LAS ACTIVIDADES QUE PERSIGUE LA SOCIEDAD.

CERTIFICA:

?RGANOS DE DIRECCI?N Y ADMINISTRACI?N. PARA LOS FINES DE SU DIRECCI?N, ADMINISTRACI?N Y REPRESENTACI?N, LA SOCIEDAD TIENE LOS SIGUIENTES ?RGANOS: A) ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) TRES VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS.

LA DIRECCI?N DE LA SOCIEDAD CORRESPONDE, EN PRIMER TERMINO A LA ASAMBLEA GENERAL DE ACCIONISTAS Y EN SEGUNDO LUGAR, A LA JUNTA DIRECTIVA COMO DELEGADA DE AQUELLA.

LA REPRESENTACI?N LEGAL DE LA SOCIEDAD Y LA GESTI?N DE LOS NEGOCIOS SOCIALES, ESTAR?N A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS.

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSI?N DE LA SOCIEDAD, SU TRANSFORMACI?N, LA ENAJENACI?N O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCI?N O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACI?N MODIFICACI?N DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICI?N DE ACCIONES PROPIAS, CON SUJECI?N A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTER?S DE LA SOCIEDAD.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA

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COMO REPRESENTANTES LEGALES DE LA COMPA??A EN JUICIO Y FUERA DE JUICIO, LOS REPRESENTANTES TIENEN FACULTADES PARA EJECUTAR O CELEBRAR SIN OTRAS LIMITACIONES QUE LAS ESTABLECIDAS EN LOS ESTATUTOS EN CUANTO SE TRATE DE OPERACIONES QUE DEBAN SER PREVIAMENTE AUTORIZADAS POR LA JUNTA DIRECTIVA O POR LA ASAMBLEA DE ACCIONISTAS, TODOS LOS ACTOS O CONTRATOS COMPRENDIDOS DENTRO DEL OBJETO SOCIAL O QUE TENGAN CAR?CTER SIMPLEMENTE PREPARATORIO, ACCESORIO O COMPLEMENTARIO PARA LA REALIZACI?N DE LOS FINES QUE PERSIGUE LA SOCIEDAD Y LOS QUE SE RELACIONAN DIRECTAMENTE CON LA EXISTENCIA Y EL FUNCIONAMIENTO DE LA MISMA. LOS REPRESENTANTES QUEDAN INVESTIDOS DE PODERES ESPECIALES PARA TRANSIGIR, ARBITRAR Y COMPROMETER LOS NEGOCIOS SOCIALES; PROMOVER O COADYUVAR ACCIONES JUDICIALES, ADMINISTRATIVAS O CONTENCIOSO ADMINISTRATIVAS EN QUE LA COMPA??A TENGA INTER?S E INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES CONFORME A LA LEY; DESISTIR DE LAS ACCIONES O RECURSOS QUE INTERPONGAN; NOVAR OBLIGACIONES O CR?DITOS; DAR O RECIBIR BIENES EN PAGO; CONSTITUIR APODERADOS JUDICIALES O EXTRAJUDICIALES, DELEGARLES FACULTADES REVOCAR MANDATOS Y SUSTITUCIONES.

PARAGRAFO: LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN AMPLIAS FACULTADES, SIN NINGUNA LIMITACI?N Y SIN REQUERIR AUTORIZACI?N PREVIA DE LA JUNTA DIRECTIVA, PARA ACTUAR EN NOMBRE DE LA SOCIEDAD EN LICITACIONES PUBLICAS, PRIVADAS O CUALQUIER OTRA MODALIDAD DE CONTRATACI?N, PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES Y CONTRATAR SIN LIMITACI?N DE CUANT?A ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOM?A MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRITAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA:

DOCUMENTO: ACTA No. 393 DEL 20 DE ENERO DE 1993
ORIGEN: JUNTA DIRECTIVA
INSCRIPCION: 26 DE ENERO DE 1993 No. 62203 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

PRESIDENTE EJECUTIVO
FRANCISCO JOSE BARBERI OSPINA
C.C.14445880

VICEPRESIDENTE EJECUTIVO
JUAN MANUEL BARBERI OSPINA
C.C.14949561

VICEPRESIDENTE EJECUTIVO
JUAN BAUTISTA DE LOS RIOS GUTIERREZ

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C.C.16615708

SUPLENTES

PRIMER RENGLON
GUSTAVO ADOLFO SANCHEZ LESMES
C.C.16625960

SEGUNDO RENGLON
VICTOR RICARDO ROSA GARCIA
C.C.6811102

TERCER RENGLON
ANTONIO JAIRO RAMIREZ ECHAVE
C.C.16741040

CUARTO RENGLON
ERNESTO TRUJILLO PEREZ
C.C.14984104

QUINTO RENGLON
ANA MARIA ALVAREZ
C.C.31170896

CERTIFICA:

DOCUMENTO: ACTA No. 59 DEL 31 DE MARZO DE 2003
ORIGEN: ASAMBLEA DE ACCIONISTAS
INSCRIPCION: 23 DE ABRIL DE 2003 No. 2845 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL
DELOITTE & TOUCHE LTDA D & T LTDA
NIT.860005813-4

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AGOSTO DE 2004
ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA
INSCRIPCION: 30 DE AGOSTO DE 2004 No. 9417 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

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QUE POR ESCRITURA NRO. 2719 DEL 15 DE JULIO DE 1999 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE AGOSTO DE 1999 BAJO EL NRO. 323 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A SAMUEL GOMEZ UPEGUI, MAYOR DE EDAD, VECINO DE CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 16.633.490, GERENTE DEL DISTRITO DE VENTAS DEL OCCIDENTE COLOMBIANO DE LA SOCIEDAD, CON SEDE EN CALI, UBICADO EN LA CALLE 23 NRO. 4-66, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO O POLICIVO, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES DE CARACTER LABORAL, CIVIL, COMERCIAL Y POLICIVO, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESA FACULTAD PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRAPROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 4) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 5) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPENO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion : 02NBM1226042 PAGINA No. 13

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LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARAGRAFO. LA FACULTAD PARA TRANSIGIR O CONCILIAR SE LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 5o.) OTORGUE PODERES Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARACTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACION DE LOS CREDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TITULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CREDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUIMICAS S.A. A LAS AUDIENCIAS DE CONCILIACION QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACION PARA TRANSIGIR, DESISTIR CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTE A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS NORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTE A TECNOQUIMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACION QUE LOS DEUDORES DE LA SOCIEDAD CONVOQUEN ANTE LAS ENTIDADES FACULTADAS PARA ELLO CON EL FIN OBTENER UN ACUERDO EN EL PAGO DE LAS ACREENCIAS, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER Y RECIBIR, FACULTADES QUE SE LIMITAN HASTA POR LA SUMA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. 8o.) REVISE LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARACTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACION DE SUS ACREENCIAS. 9o.) APRUEBE Y SUSCRIBA ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUIMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MINIMOS LEGALES MENSUALES.

CERTIFICA:

QUE POR ESCRITURA NRO. 309 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 300 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A DANIEL AMEZQUITA, MAYOR DE EDAD, VECINO DE BARRANQUILLA,

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PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 310 DEL 31 DE ENERO DE 2002 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO DE 2002 BAJO EL NRO. 301 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE A CARLOS ORLANDO MUTIS, MAYOR DE EDAD, VECINO DE BUCARAMANGA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 91.200.418 DE BUCARAMANGA, GERENTE DEL DISTRITO DE VENTAS DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES: 1) PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A. Y EN ASUNTOS QUE TENGA QUE VER CON EL DISTRITO DE VENTAS SE NOTIFIQUE Y PROMUEVA ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO, Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE. PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES. 2) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL ANTERIOR. 3) PARA QUE OTORGUE PODER Y CONSTITUYA MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DIVERSAS AUDIENCIAS CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD

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CAMARA DE COMERCIO DE BOGOTA

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RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO. 4) PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO. 5) PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A. EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPENO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO, HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. PARAGRAFO: ES ENTENDIDO QUE EL APODERADO, EN SU CONDICION DE GERENTE, ESTA FACULTADO PARA REALIZAR LA VENTA, SIN LIMITACION DE CUANTIA, DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

QUE POR ESCRITURA NRO. 4.202 DEL 31 DE MAYO DE 1995 NOTARIA DECIMA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTIEMBRE DE 2003 BAJO EL NRO. 134 DEL LIBRO V SE CONFIERE PODER ESPECIAL A ANTONIO JAIRO RAMIREZ ECHAVE, ABOGADO TITULADO Y EN EJERCICIO, CON TARJETA PROFESIONAL No. 58.401 DEL MINISTERIO DE JUSTICIA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 16.741.040 DE CALI PARA QUE REPRESENTE A TECNOQUIMICAS S.A., EN LOS SIGUIENTES ACTOS: A) SOLICITAR Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES ATINENTES A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL; B) TODOS LOS TRAMITES ANTE EL INVIMA ATINENTES A LA OBTENCION DE REGISTRO SANITARIO, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRA LINEA DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, CESIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER Y VICEVERSA, E IGUALMENTE CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS, A CUYO OBJETO LO FACULTO PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS, PRESENTAR SOLICITUDES, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR APELACIONES Y RECLAMOS, DESISTIR Y PERCIBIR. ASI MISMO DICHO APODERADO ESTA AUTORIZADO PARA HACER CUANTO FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS INCLUIDAS LAS DE SUSTITUIR Y DELEGAR EL

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DE BOGOTA, QUIEN ACTUA EN SU CALIDAD DE REPRESENTANTE LEGAL DE TECNOQUIMICAS S. A. SOCIEDAD COMERCIAL ORGANIZADA Y EXISTENTE CONFORME A LAS LEYES COLOMBIANAS, CON DOMICILIO Y SEDE PRINCIPAL EN CALI. EN DICHA CONDICION CONFIERE PODER AMPLIO Y SUFICIENTE A LAS SIGUIENTES PERSONAS: CLAUDETTE VERNOT HERNANDEZ ABOGADA TITULADA Y EN EJERCICIO, IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 51722517 DE BOGOTA, PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADO No. 57111 DEL C.S. DE LA J., ANDRES FELIPE ZAPATA OCAMPO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79598546 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 107240 DEL C.S. DE LA J. Y JUAN MANUEL SERRANO CASTILLO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79875670 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 124953 DE C.S. DE LA J., TODOS CON DOMICILIO EN LA CIUDAD DE BOGOTA, D.C., PARA QUE EN NOMBRE DE MI REPRESENTADA ACTUEN EN TODOS LOS ASUNTOS DE PROPIEDAD INTELECTUAL Y LOS DERIVADOS DE ELLA, CON FACULTAD PARA RECIBIR NOTIFICACIONES, NOMBRAR APODERADOS JUDICIALES O EXTRAJUDICIALES EN ESTOS ASUNTOS.

EL PRESENTE PODER SE CONFIERE PARA QUE LOS APODERADOS ACTUEN ANTE CUALQUIER PERSONA O AUTORIDAD ADMINISTRATIVA DEL ORDEN NACIONAL, DEPARTAMENTAL, DISTRITAL Y LOCAL; ANTE LAS AUTORIDADES CONTENCIOSO ADMINISTRATIVAS Y JUDICIALES, PARA OBTENER LA PROTECCION DE NUESTRA PROPIEDAD INTELECTUAL Y CONTRA LAS PRACTICAS RESTRICTIVAS DE LA COMPETENCIA Y LOS ASUNTOS DE COMPETENCIA DESLEAL, A CUYO EFECTO LA AUTORIZO, EN TODO LO CONCERNIENTE A LOS SIGUIENTES ASUNTOS: A) OBTENCION DE PATENTES DE INVENCION, DE MODELO DE UTILIDAD, ESQUEMAS DE TRAZADOS DE CIRCUITOS INTEGRADOS, DISE?OS INDUSTRIALES, EL REGISTRO DE MARCAS DE PRODUCTOS O SERVICIOS; LEMAS COMERCIALES; DEPOSITO DE NOMBRES Y ENSE?AS COMERCIALES, INDICACIONES GEOGRAFICAS; RENOVACION DE SIGNOS DISTINTIVOS, RENOVACIONES, AFECTACIONES AL REGISTRO, INSCRIPCION DE CONTRATOS, SOLICITUD Y RENOVACION DE NOMBRES DE DOMINIO; B) PRESENTACION DE OPOSICIONES AL REGISTRO DE MARCAS DE TERCERO, PRESENTACION DE ALEGATOS EN DEFENSA DE OPOSICIONES AL REGISTRO, ACCION DE CANCELACION, ACCION POR INFRACCION DE DERECHOS, REVOCATORIA DIRECTA, ACCION DE NULIDAD, ACCION DE NULIDAD Y RESTABLECIMIENTO DEL DERECHO, ACCION REIVINDICATORIA, ACCIONES DE TUTELA, POPULARES, DE GRUPO, DE CLASE; ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; C) AGOTAMIENTO DE LA VIA GUBERNATIVA, EJERCICIO DEL DERECHO DE PETICION ANTE CUALQUIER PERSONA O AUTORIDAD; D) SOLICITUD DE MEDIDAS CAUTELARES, PRESENTACION DE ACCIONES MEDIANTE PROCESOS CIVILES, PENALES, ADMINISTRATIVOS O CONTENCIOSO ADMINISTRATIVOS RELACIONADOS CON ESTOS DERECHOS U OTROS DE DIFERENTE NATURALEZA, MEDIDAS EN FRONTERA, ACCIONES Y PROCESOS QUE PROMOVAMOS O SE NOS PROMUEVAN; E) OBTENER Y TRAMITAR TODO LO RELACIONADO CON EL RECONOCIMIENTO DE DERECHOS DE AUTOR, DERECHOS CONEXOS Y NUEVAS TECNOLOGIAS Y SU PROTECCION LEGAL; F) SOLICITUD DE REGISTRO Y RENOVACION DE CONTRATOS DE TRANSFERENCIA DE TECNOLOGIA; G) OBTENER Y TRAMITAR TODO LO RELACIONADO CON LICENCIAS DE FUNCIONAMIENTO, REGISTROS SANITARIOS, AUTORIZACION DE CERTIFICADOS DE LIBRE VENTA, AUTORIZACION DE PUBLICIDAD ANTE EL MINISTERIO DE PROTECCION SOCIAL O EL INVIMA O ANTE CUALQUIER AUTORIDAD SANITARIA; H) OBTENCION DE CERTIFICADOS DE CARENCIA DE INFORMES POR TRAFICO DE ESTUPEFACIENTES.RENOVACIONES, AUTORIZACIONES EXTRAORDINARIAS ANTE LA DIRECCION NACIONAL DE ESTUPEFACIENTES O EL CONSEJO NACIONAL DE ESTUPEFACIENTES; I)

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DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A., EN NINGUN CASO, QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES. 6) PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO EJERZA LAS SIGUIENTES FACULTADES ESPECIALES: A) COMPRAR Y PERMUTAR TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPE?O DE LAS ACTIVIDADES DEL ESTABLECIMIENTO HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. B) MANEJAR LAS CUENTAS CORRIENTES CON FACULTADES PARA GIRAR CHEQUES HASTA POR LA CUANTIA QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. C) OTORGAR CREDITOS EN DESARROLLO DE LAS VENTAS DE LOS ARTICULOS PROPIOS DE LA ACTIVIDAD COMERCIAL DEL DISTRITO DE VENTAS, DE ACUERDO CON LO QUE DETERMINEN LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD. D) RECIBIR A NOMBRE DE LA SOCIEDAD CUALQUIER SUMA DE DINERO, EXPIDIENDO LOS COMPROBANTES EN QUE CONSTE EL PAGO.

CERTIFICA:

CAPITAL AUTORIZADO: $27,200,000,000
NUMERO DE ACCIONES: 54,400,000
VALOR NOMINAL: $500
CAPITAL SUSCRITO: $27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: $500
CAPITAL PAGADO: $27,123,804,000
NUMERO DE ACCIONES: 54,247,608
VALOR NOMINAL: $500

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.158 DEL LIBRO IX, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

CONTROLADA: INDUGRAFICAS S.A.
DOMICILIO: CALI
NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE INDUGRAFICAS S.A. CORRESPONDEN AL DESARROLLO DE NEGOCIOS RELACIONADOS CON LAS ARTES GRAFICAS, LA DISTRIBUCION DE LAS MISMAS YA SEA DE SUS PRODUCTOS PROPIOS O POR CONTRATO, TANTO EN EL MERCADO NACIONAL COMO

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20071226 Hora Certificado 13:56:33

Operacion : 02NBM1226042 PAGINA No. 23

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ACTIVIDAD: LAS ACTIVIDADES DE TECNOQUIMICAS CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION DE PRODUCTOS BIOLOGICOS, QUIMICOS, MEDICAMENTOS Y PRODUCTOS FARMACEUTICOS, PANALES, PRODUCTOS VETERINARIO Y AGRICOLAS, ALIMENTOS, COSMETICOS Y DE TOCADOR Y PRODUCTOS DE ASEO PARA EL HOGAR.

SUBORDINADA: ADHESIVOS INTERNACIONALES S.A.- ADHINTER S.A. DOMICILIO: CALI VALLE DEL CAUCA
NACIONALIDAD: COLOMBIANA
ACTIVIDAD: LAS ACTIVIDADES DE ADHINTER S.A. SE DESARROLLAN EXCLUSIVAMENTE EN LA ZONA FRANCA DEL PACIFICO CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION EN EL MERCADO NACIONAL E INTERNACIONAL DE ADHESIVOS MEDICINALES TALES COMO CURAS, VENDITAS, ESPARADRAPOS, PARCHES, VENDAS; ADHESIVOS PARA USO EN OFICINA TALES COMO CINTAS, PEGANTES, PAPELES ADHESIVOS Y CINTAS ADHESIVAS PARA USO INDUSTRIAL.

PRESUPUESTO DE CONTROL: TECNOQUIMICAS S.A., TIENE SUSCRITAS EN LA SOCIEDAD ADHESIVOS INTERNACIONALES S.A. ADHINTER S.A., LA CANTIDAD DE DOS MILLONES CUATROCIENTOS TREINTA MIL (2.430.000) ACCIONES ORDINARIAS DE VALOR NOMINAL DE CIEN PESOS ($100.00) SOBRE UN TOTAL DE TRES MILLONS (3.000.000) DE ACCIONES ORDINARIAS SUSCRITAS QUE REPRESENTA UNA PARTICIPACION DIRECTA DEL 81% SOBRE EL TOTAL DEL CAPITAL SUSCRITO Y PAGADO DE LA SOCIEDAD.

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.7050-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: ---C 23 7 39 DE CALI
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311234-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: -K 7 22 122 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992
RENOVO : POR EL A?O 2007

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.311235-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: -C 23 4 66 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20071226 Hora Certificado 13:56:33

Operacion : 02NBM1226042 PAGINA No. 25

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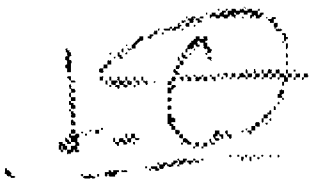


8823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-068181--00005-0000
Fecha: 2008-01-30 Dep. 2020 NUECREACIONE
Tra 11 PATENTE Y... Eve: 378 FASENACIONALI
Act 400 OFOSIOBSERVTER Folios: 89

RECIBO OFICIAL DE CAJA : 08 - 6,799
FECHA : ENERO 25 DE 2008

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
..YES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2661622	24/01/2008	266,000.00

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

CANT.	RENTISTICO		CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
			TOTAL : $	266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

..ONSABLE : ____________________

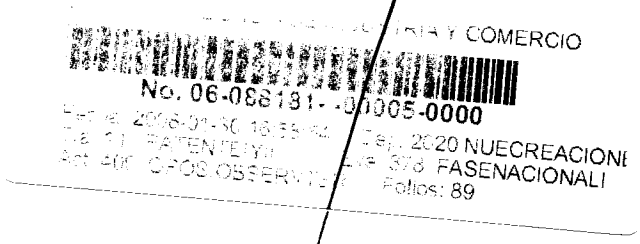
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. ____________________

8/9 255

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 8,077
FECHA : ENERO 30 DE 2008



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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2661946	30/01/2008	266,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
		TOTAL :	$ 266,000.00

N: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

256

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 7[illegible]5

ASUNTO:

Radicación PCT Nº	06-88181
Trámite	011
Evento	379
Actuación	440
Folios	010

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

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

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

El anterior oficio fue notificado por fijación en lista de fecha, 30 MAR 2020.

202021

257

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Emilio Ferrero
Apoderado

Oficio N°: 7106

ASUNTO:

Radicación PCT Nº	06-88181
Trámite	011
Evento	379
Actuación	440
Folios	078

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de las sociedades Tecnoquímicas S.A., y Laboratorio Franco Colombiano Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

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

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

202021