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Art. 400 OPOSIOBSLRVIER Folios 67

FORMULARIO UNICO DE OPOSICION
2000-12

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OPOSICION A:

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

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**SOLICITUD
PUBLICADA**

Número del expediente: 07 032.749
Solicitante: SCOLR PHARMA, INC.
Apoderado: LAURA MICHELSEN NIÑO
Título de la nueva creación o denominación del signo:
**FORMA FARMACÉUTICA DE IBUPROFENO DE LIBERACIÓN
MODIFICADA.**
Gaceta: 594 de 31/07/2008 Número de Publicación 611.

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OPOSICION PRESENTADA POR:

OPOSITOR	Nombre: TECNOQUIMICAS S.A., Sociedad comercial organizada y existente a las leyes Colombianas, con domicilio y sede principal en la Ciudad de Cali Valle Dirección: Calle 23 # 7-39 Cali - Valle Teléfono: 882 5555 Fax: 883 8859 E-mail: Domicilio: Cali - Valle	IDENTIFICACION C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890.300.466-5
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar Dirección: Cra. 17 No. 88-23, Of. 205 Teléfono: (1) 621.26.31 E-mail: info@reyes-abogados.com Fax: (1) 621.25.42 Domicilio: Bogotá, D.C.	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655

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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 susceptibles de aplicación industrial), y 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia)). Artículo 30 (Reivindicaciones) y artículo 42 (oposiciones) de la Decisión 486 de la Comisión de la Comunidad Andina.

Justificación: Ver Anexo

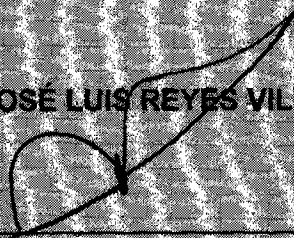
5 Comprobante de pago No. 08-85311
08-85313 (Oposición) Fecha Octubre 28/2008
(Prórroga) Fecha Octubre 28/2008

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: 

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E. S. D.

REF: Expediente 07-032-749

TÍTULO SOLICITADO: FORMA FARMACÉUTICA DE IBUPROFENO DE
LIBERACIÓN MODIFICADA.

PUBLICACIÓN: Gaceta 594 de 31 de Julio de 2008, N° de publicación
611.

PRIORIDAD: US 60/614.932 de 30/09/2004

SOLICITANTE: SCOLR PHARMA, INC.

APODERADO: LAURA MICHELSEN NIÑO

TRÁMITE: PRESENTACIÓN DE OPOSICION

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 la sociedad **TECNOQUÍMICAS 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 **07-032-749**, por no cumplir con lo dispuesto por los artículos 14, 18 y 20 literal d) de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

Asiste a **TECNOQUÍMICAS 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. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud en curso que se refiere a una forma farmacéutica sólida (tableta/comprimido) para la administración oral modificada de ibuprofeno que comprende un polímero hidrofílico, de 300 a 800 mg de ibuprofeno uniformemente dispersos en dicho polímero, una sal alcalina, croscarmelosa, y un aditivo que puede ser celulosa microcristalina, sílice, estereato de magnesio, ácido esteárico, lactosa, almidón pregetalinizado, fosfato dicálcico, un aminoácido o combinación de los mismos; carece por completo de los requisitos fundamentales para otorgársele el privilegio de patente de invención, tal y como lo demuestran los siguientes argumentos:

- 3.1. En el estado de la técnica se encuentran documentos que describen formulaciones sólidas de administración oral con liberación modificada de Ibuprofeno con algunas de las características que se reivindican en la solicitud colombiana en trámite. Es el caso por ejemplo de la publicación internacional WO 03/063825 (publicada el 07 de Agosto de 2003) en cuyo capítulo reivindicatorio se hace mención al uso de agentes alcalinos, hidroxipropilmetilcelulosa y polímeros hidrosolubles dentro de la formulación; en la patente americana US 4,877,620 (publicada el 31 de Octubre de 1989) por ejemplo se hace mención de la inclusión de aminoácidos; y por su parte la publicación internacional WO 88/08299 (publicada el 03 de Noviembre de 1988) incluye excipientes como croscarmelosa, estereato de magnesio, ácido esteárico, dióxido de silicio (Sílice), celulosa microcristalina y almidón

pregetalinizado, también, en formulaciones de liberación modificada de ibuprofeno.

Finalmente la patente Europea EP 0297866 publicada el 04 de Enero de 1987 y titulada "THERAPEUTIC AGENTS" revela:

1. A sustained release pharmaceutical composition which comprises granules comprising a homogeneous mixture of ibuprofen and a pharmaceutically acceptable polymeric material operable to provide a slow release of ibuprofen over a pH range from 1.0 to 7.5, the polymeric material being present in an amount of 5% to 25% by weight, based on the weight of the ibuprofen.

2. A pharmaceutical composition according to claim 1 in which the polymeric material is present in an amount of 5% to 15% by weight, based on the weight of the ibuprofen.

3. A pharmaceutical composition according to claim 1 or claim 2 in which the polymeric material comprises ethyl cellulose, a copolymer of dimethylaminoethyl methylacrylate and methacrylic acid ester or high viscosity hydroxy propyl methyl cellulose.

(...)

6. A tablet which comprises granules comprising a homogeneous mixture of ibuprofen and ethyl cellulose, the ethyl cellulose being present in an amount of 5% to 15% by weight, based on the weight of ibuprofen.

(...)

9. A process for the preparation of sustained release granules comprising ibuprofen and a pharmaceutically acceptable polymeric material operable to provide a slow release of the ibuprofen over the pH range 1.0 to 7.5, the polymeric material being present in an amount of 5% to 25% by weight, based on the weight of ibuprofen, which comprises dissolving the ibuprofen and the polymeric material in a solvent and evaporating the solvent to form granules of coprecipitated ibuprofen and polymeric material.

10. A process according to claim 9 for the production of granules according to any one of claims 1 to 4.

11. A process for the production of tablets which comprises the compression of granules prepared by the process of claim 10.

En este documento se puede evidenciar el uso de un polímero hidrofílico, - específicamente hidroxipropilmetilcelulosa de alta viscosidad- en formulaciones de liberación sostenida, en donde se dispersa uniformemente el ibuprofeno y el rango de cantidades en que se encuentra presente dicho polímero, tal como se revela en la solicitud colombiana en trámite.

3.2. En otro aspecto, existen también documentos donde se revela que a través de formulaciones farmacéuticas del mismo tipo que las descritas por la solicitud colombiana en trámite (formulaciones sólidas tipo tableta de liberación modificada de ibuprofeno para administración oral), se consigue modificar el tiempo de liberación de ibuprofeno dentro del mismo rango de tiempo en que lo consigue la formulación de dicha solicitud colombiana, o en algunos casos, mas allá de dichos rangos. Por ejemplo la publicación

internacional WO 99/12524 (publicada el 18 de Marzo de 1999) revela en su capítulo reivindicatorio que sus formulaciones sólidas tipo tableta de liberación modificada de ibuprofeno para administración oral consiguen dentro de 9 horas una liberación del 50-100%, 60-98%, 65-95%, 70-90% o 70-80% de ibuprofeno, lo que coincide con lo expuesto por la formulación colombiana en trámite que libera un 20% en las primeras 2 horas, con la posterior liberación constante durante 8 horas y en donde al menos el 70% del ibuprofeno se libera a lo largo de un periodo no superior a 14 horas.

Por su parte la patente europea EP 0313328 (publicada el 26 de Abril de 1989) menciona un periodo de liberación modificada de ibuprofeno de 12 horas y además incluye en la formulación derivados de celulosa hidroxilados solubles en agua tal como la hidroxipropilmetilcelulosa.

Finalmente la publicación internacional WO 98/01117 (publicada el 15 de Enero de 1998) revela periodos de tiempo de 12 a 16 horas partiendo de 500 a 1000 mg de ibuprofeno, que además, es un rango de cantidad incluido o mencionado dentro del rango de cantidad de ibuprofeno reivindicado por la solicitud colombiana (300 a 800 mg).

Si se tiene en cuenta que el nivel inventivo se define sobre el problema técnico a solucionar, en este caso la liberación sostenida de ibuprofeno, es evidente que las diferencias técnicas aportadas por lo reivindicado en la solicitud colombiana en trámite dan una solución a un problema técnico que ya había sido resuelto en el mismo estado de la técnica de manera apreciablemente similar y/o superior.

En otras palabras, las formulaciones farmacéuticas de liberación modificada de ibuprofeno contenidas en el capítulo reivindicatorio de la solicitud colombiana en trámite carecen de nivel inventivo, primero, por tratarse de formulaciones cuya composición, si bien no se encuentra descrita en su totalidad en el estado de la técnica, se pueden encontrar varios de sus componentes y sus características incluidas en formulaciones del mismo tipo (liberación modificada de ibuprofeno); y por último, porque busca darle solución a un problema ya resuelto en el estado de la técnica de una manera menos efectiva.

3.3. Para finalizar, la solicitud colombiana en trámite, específicamente en sus reivindicaciones 20 a 24 revela un método para mantener una concentración media de al menos 6,4 microgramos/ml en plasma de ibuprofeno en un paciente durante un periodo de tiempo de 2 a 8 horas, lo cual a la luz de la Decisión 486 de la Comunidad Andina de Naciones es inaceptable, ya que en su aparte d) del artículo 20 del capítulo I, acerca de los requisitos de patentabilidad, expone explícitamente que no serán patentables *“los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos y a los animales”*, y si tenemos en cuenta que la solicitud en trámite lo que reivindica en las reivindicaciones señaladas es precisamente un método de tratamiento, queda claramente expuesta la improcedencia para otorgar el privilegio de patente a esta solicitud.

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, 18 y 20 literal d) de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. SOLICITUD DE PLAZO EXTRA PARA SUSTENTAR LA OPOSICIÓN

En desarrollo de lo dispuesto por el artículo 42, inciso 2º de la Decisión 486, solicito comedidamente a su Despacho el plazo adicional de sesenta días para sustentar la presente oposición. Para los anteriores efectos, me permito anexar la constancia de pago correspondiente.

VI. 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:

- ❖ Portadas y capítulos reivindicatorios de todas las publicaciones mencionadas en el acápite de Fundamentos de la Oposición.

VII. ANEXOS

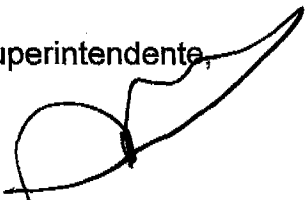
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de Tecnoquímicas S.A.
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.

VIII. 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.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

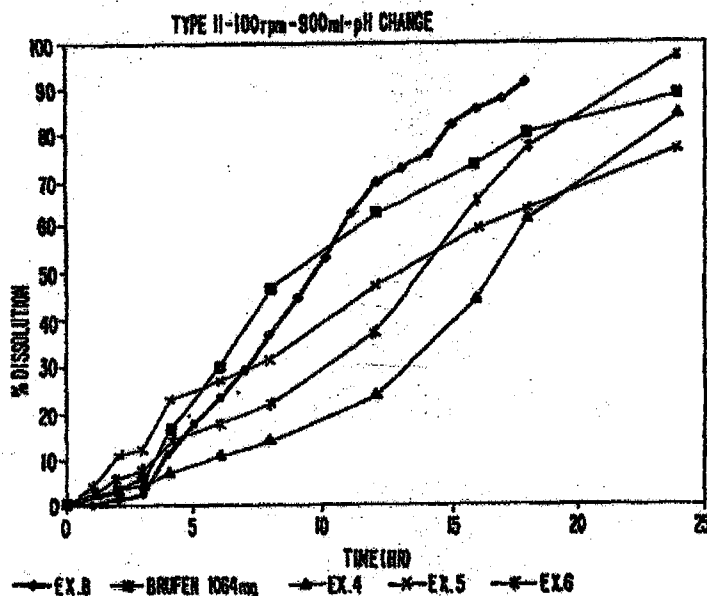


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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6: A61K 9/20	A1	(11) International Publication Number: WO 98/01117
		(43) International Publication Date: 15 January 1998 (15.01.98)
(21) International Application Number: PCT/US97/13331		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 8 July 1997 (08.07.97)		
(30) Priority Data: 60/021,335 8 July 1996 (08.07.96) US		
(71) Applicant (for all designated States except US): EDWARD MENDELL CO., INC. [US/US]; 2981 Route 22, Patterson, NY 12563 (US).		
(72) Inventor; and (75) Inventor/Applicant (for US only): BAICHWAL, Anand, R. [IN/US]; 5 Kendell Drive, Wappinger Falls, NY 12590 (US).		
(74) Agents: DAVIDSON, Clifford, M. et al.; Steinberg, Raskin & Davidson, P.C., 1140 Avenue of the Americas, New York, NY 10036 (US).		Published With international search report.

(54) Title: **SUSTAINED RELEASE MATRIX FOR HIGH-DOSE INSOLUBLE DRUGS**



(57) Abstract

Sustained release dosage forms of high dose insoluble drugs such as ibuprofen and methods for their manufacture are disclosed.

WHAT IS CLAIMED IS:

1. A sustained release dosage form, comprising from about 500 mg to about 1000 mg of an insoluble NSAID and an effective amount of a sustained release carrier, said dosage form releasing providing a dissolution of said NSAID in-vitro when measured by the USP Type II (Paddle) Method, of from about 6 percent by weight of said NSAID released after about 2 hours and a t_{50} after about 12 to about 16 hours.
2. The dosage form of claim 1, wherein said sustained release carrier comprises xanthan gum and a crosslinking agent.
3. The dosage form of claim 2, wherein said crosslinking agent is a galactomannan.
4. The dosage form of claim 3, wherein said galactomannan is locust bean gum.
5. The dosage form of claim 1, further comprising an inert diluent.
6. The dosage form of claim 1, wherein said NSAID is selected from the group consisting of ibuprofen, calcium fenoprofen, naproxen, etodolac, mefenamic acid, tolmetin, and mixtures thereof.
7. The dosage form of claim 1, wherein said NSAID is ibuprofen.
8. The dosage form of claim 1, which is in the form of a tablet.

9. The dosage form of claim 2, wherein said cross-linking agent comprises a galactomannan gum, an ionizable gel strength enhancing agent, or a combination thereof.

10. A sustained release dosage form, comprising from about 500 mg to about 1000 mg of an insoluble NSAID and an effective amount of a sustained release carrier, said dosage form releasing providing a dissolution of said NSAID in-vitro when measured by the USP Type II (Paddle) Method, of from about 20 percent by weight of said ibuprofen released after about 4 hours and a t_{50} after about 12 to about 16 hours.

11. The dosage form of claim 10, wherein said sustained release carrier comprises xanthan gum and a crosslinking agent.

12. The dosage form of claim 11, wherein said crosslinking agent is a galactomannan.

13. The dosage form of claim 12, wherein said galactomannan is locust bean gum.

14. The dosage form of claim 11, further comprising an inert diluent.

15. The dosage form of claim 10, wherein the said NSAID is selected from the group consisting of ibuprofen, calcium fenoprofen, naproxen, etodolac, mefenamic acid, tolmetin, and mixtures thereof.

16. The dosage form of claim 10, wherein the said NSAID is ibuprofen.

17. The dosage form of claim 12, wherein said cross-linking agent comprises a galactomannan gum, an ionizable gel strength enhancing agent, or a combination thereof.

18. A sustained release ibuprofen dosage form comprising about 500 mg to about 1000 mg ibuprofen; a sustained release coating comprising a hydrophobic material; and a tablet core comprising xanthan gum; wherein from about 1 to about 20 percent by weight of said ibuprofen is coated on said tablet, said dosage form releasing providing a dissolution of said NSAID in-vitro when measured by the USP Type II (Paddle) Method, of from about 6 percent by weight of said NSAID released after about 2 hours and a t_{50} after about 12 to about 16 hours.

19. An oral sustained release dosage form, comprising
a matrix comprising from about 500 to about 1000 mg of ibuprofen and a sustained release carrier comprising about 5 to about 95% xanthan gum and a crosslinking agent comprising locust bean gum; wherein the weight ratio of said ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4.

20. The oral sustained release dosage form of claim 19, comprising wherein the weight ratio of said NSAID to the combined weight of said xanthan gum and said locust bean gum is from about 0.08 to about 0.25.

21. The oral sustained release tablet of claim 19 composing from about 800 to about 1000 mg ibuprofen.

22. A method of preparing an oral sustained release dosage form comprising the steps of
wet granulating a mixture of xanthan gum, locust bean gum, an inert diluent

and an insoluble ibuprofen in a ratio of xanthan gum to locust bean gum is from about 1:20 to about 20:1 and in a ratio of the total weight of ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4; and

tableting the resulting granulate into tablets containing from about 500 to about 1000 mg of ibuprofen.

23. A sustained release pharmaceutical excipient for use in oral solid dosage forms, comprising xanthan gum, a galactomannan capable of cross-linking said xanthan gum in the presence of aqueous solutions, and from about 20 to about 35 percent by weight of an inert diluent.

24. A sustained release tablet comprising
from about 500 mg to about 1000 mg of an insoluble NSAID in a sustained release matrix comprising xanthan gum and locust bean gum, wherein the total weight of said tablet is from about 110 percent to about 140 percent by weight of said insoluble NSAID, said xanthan gum and said locust bean gum comprising from about 7 to about 40 percent by weight of the tablet.

25. The sustained release tablet of claim 24, wherein said NSAID is ibuprofen and the combined weight of said xanthan gum and said locust bean gum is from about 119 percent to about 136 percent of ibuprofen.

26. A method of retarding the release of ibuprofen from a sustained release ibuprofen tablet containing xanthan gum when the tablet is exposed to an aqueous environment comprising replacing from about 5 to about 95 percent by weight of the xanthan gum in the sustained release ibuprofen tablet with a weight equivalent amount of locust bean gum, wherein the ratio of said xanthan gum to said locust bean gum ranges from about 1:20 to about 20:1.

27. A sustained release ibuprofen tablet comprising from about 600 to about 1000 mg ibuprofen; xanthan gum; locust bean gum; and an inert diluent; wherein the combined weight of said xanthan gum and said locust bean gum is from about 7 to about 40 percent by weight of the final tablet weight and the ratio of ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.06 to about 1:0.4.

28. A sustained release ibuprofen tablet of claim 27 wherein the ratio of ibuprofen to the combined weight of said xanthan gum and said locust bean gum is from about 1:0.08 to about 1:0.25.

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 88309802.2

(51) Int. Cl.⁴: **A 61 K 9/46**
A 61 K 9/52

(22) Date of filing: 19.10.88

(30) Priority: 22.10.87 GB 8724763

(43) Date of publication of application:
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(84) Designated Contracting States:
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(84) Sustained-release formulations.

(57) A granular sustained-release formulation of a pharmacologically active substance presented in the form of a tablet, said tablet comprising sufficient granules to provide a predetermined dose or number of doses of the pharmacologically active substance and effervescent or water-dispersible ingredients, each of said granules having a diameter of preferably between 0.5 and 2.5 mm and comprising:

a) a core comprising one or more pharmacologically active substances with preferably one or more excipients; and

b) a coating covering substantially the whole surface of the core and comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of the coating being from 2 to 25% of the weight of the core.

A method for preparing this effervescent or water-dispersible tablet formulation is also provided. Such formulations enable large dosages in sustained-release form to be more easily administered to patients.

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185(b) Manufacture of granules

Mefenamic acid B.P.	20.0g	5
Tween 80 (4% solution)	5.0ml	
Microcrystalline Cellulose U.S.N.F.	1.1g	10
Water	8.0ml	

The mefenamic acid was placed in a mortar and 5.0ml of a 4% solution of Tween 80 was added in portions whilst the mixture was triturated with a pestle. The microcrystalline cellulose was then added and mixed in, followed by 1.0ml portions of water until a slightly cohesive product was obtained. This product was formed into granules by forcing it into circular holes (2mm diameter) in a perspex sheet (2mm thickness). The granules were removed from the mould using a 2mm cylindrical punch and were dried to constant weight at room temperature.

Preparation of coating

As for Example 7

Coating of the granules

As for Example 7

(c) Tablet formation

The mannitol granules (176 mg) and coated granules containing mefenamic acid (88 mg), were compacted to form tablets 9 mm in diameter.

Crushing strength

As for Example 1.

Disintegration test

As for Example 1.

Dissolution test

As for Example 7.

(d) Dissolution test results

Tablets with crushing strengths of 4.0 Kg and disintegration time of 170 seconds were examined. Dissolution tests were performed on samples of the water-dispersible tablets of the present invention. For comparative purposes, tests were also performed on samples of the granules (or beads) containing mefenamic acid which were not compounded into tablets. The results are shown in Figure 9. The dissolution profile for the dispersible tablet shows a slightly faster release of mefenamic acid than for the loose granules over the initial portion of the curve. After 6-7 hours, the two curves are almost identical. Thus, the sustained-release properties of the granules are essentially maintained in the dispersible tablet formulation.

Claims

1. A granular sustained-release formulation of a pharmacologically active substance presented in the form of a tablet, said tablet comprising sufficient granules to provide a predetermined dose or number of doses of the pharmacologically active substance and effervescent or water-dispersible ingredients, each of said granules having a diameter of preferably between 0.5 and 2.5 mm and comprising:

a) a core comprising one or more pharmacologically active substances and preferably one or more excipients; and

b) a coating covering substantially the whole surface of the core and comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative, the weight of the coating being from 2 to 25% of the weight of the core.

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2. A formulation as claimed in claim 1, in which the granules provide sustained-release over a period of 12 hours, wherein the diameter of said granules is between 0.7 and 1.2 mm, the coating contains from 20 to 70 parts of the water soluble hydroxylated cellulose derivative, and the weight of the coating is between 2 and 15% of the weight of the core.
- 5 3. A formulation as claimed in claim 1, in which the granules provide sustained-release over a period of 24 hours, wherein the diameter of said granules is between 0.7 and 1.2 mm, the coating contains from 20 to 70 parts of the water soluble hydroxylated cellulose derivative, and the weight of the coating is between 5 and 25% of the weight of the core.
- 10 4. A formulation as claimed in any of the preceding claims, wherein the pharmacologically active substance is ibuprofen, nifedipine, naproxen or mefenamic acid.
5. A formulation as claimed in any of the preceding claims, wherein the polymer in the coating is Eudragit NE30D.
- 15 6. A formulation as claimed in any one of the preceding claims, wherein the hydroxylated cellulose derivative in the coating is hydroxypropylmethyl cellulose having a degree of substitution of 28 to 30% of methoxy groups and 7 to 12% of hydroxy groups.
7. A formulation as claimed in any one of the preceding claims, wherein the effervescent ingredients comprise sodium bicarbonate and an organic carboxylic acid.
8. A formulation as claimed in any one of claims 1 to 6, wherein the water-dispersible ingredient comprises mannitol.
- 20 9. A method for preparing a sustained-release formulation in the form of an effervescent or water-dispersible tablet and which comprises:
- i) mixing one or more pharmacologically active substances with preferably one or more excipients;
 - ii) forming the mixture into core particles;
 - 25 iii) forming a suspension comprising 100 parts of a water insoluble but water swellable acrylic polymer and from 20 to 70 parts of a water soluble hydroxylated cellulose derivative;
 - iv) coating the said core particles with the said suspension to form granules having a diameter of preferably between 0.5 and 2.5 mm, the weight of the coating being from 2 to 25% of the weight of the core; and
 - 30 v) compressing a sufficient amount of the granules to provide a predetermined dose or number of doses of the pharmacologically active substance, together with effervescent or water-dispersible ingredients, so as to form a tablet.
10. A suspension of sustained-release granules in a non-toxic aqueous liquid formed by contacting such a liquid with a formulation as claimed in any one of claims 1 to 8.
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(54) Title: PHARMACEUTICAL COMPOSITION FOR EXTENDED/SUSTAINED RELEASE OF THERAPEUTICALLY ACTIVE INGREDIENT

(57) Abstract: A pharmaceutical composition useful for sustained/extended release of a therapeutically active ingredient to an environment of use, said composition comprises a tablet core composition consists of a therapeutically active ingredient that is weakly acidic in nature and has a limited solubility in the aqueous environment, said the therapeutically active ingredient is in immediate contact with the agents that are capable of improving the solubility of the agent within the core, for e.g., by changing the micro environmental pH of the core and the tablet core is surrounded by a release rate controlling membrane consisting of a semi-permeable membrane forming polymer, permeable membrane forming polymer, and at least one plasticizer capable of modulating the film formation properties of the polymers.

Claims

1. A pharmaceutical composition for sustained release of a therapeutically active moiety, said composition comprising a tablet core surrounded by a release rate controlling membrane, said tablet core consisting of
 - 5 (i) the therapeutically active moiety having limited solubility in the aqueous fluids, weakly acidic in nature and having a pKa between 2.5 to 7.5,
 - (ii) an alkalizing agent or a buffer compound in immediate contact with the above said therapeutically active moiety,
 - 10 (iii) an osmotically effective solute that is soluble in water and capable of exhibiting an osmotic pressure gradient across the release rate controlling membrane against the external fluids, and
 - (iv) optionally containing one or more pharmaceutically acceptable excipients and polymers,said release rate controlling membrane consisting of:
 - 15 (i) a semi-permeable membrane forming polymer which is insoluble in water but partially permeable to aqueous fluids and substantially impermeable to the core composition,
 - (ii) a permeable membrane forming polymer which is soluble in water and permeable to aqueous fluids, and to at least one of the moiety of the core composition ; and
 - 20 (iii) at least one plasticizer ranging between 2 to 60 % by weight, based on the - total weight of dry polymers.
2. The composition according to claim 1, wherein semi-permeable membrane forming polymer and permeable membrane forming polymer together with plasticizer are
25 coated on the tablet core and dried to get the release rate controlling polymer membrane.
3. A composition according to claim 1, wherein the therapeutically active moiety is a
30 drug that act on peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular, smooth muscles, blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine and hormone system, immunological system, reproductive system, skeletal system, autocoid systems, alimentary and excretory systems, inhibitory or autocoids and histamine systems, and those materials that act on the central nervous system such as hypnotics and sedatives.

4. A composition according to claim 1, wherein the therapeutically active moiety is selected from a group consisting of acetazolamide, acetyl salicylic acid, p-amino salicylic acid, captopril, carbenicillin, carbenoxolone, chlorpropamide, clofibrate, diclofenac, diflunisal, ethacrynic acid, etodolac, fenoprofen, furosemide, glimepiride, glipizide, glyburide, ibuprofen, indomethacin, ketoprofen, naproxen, nimesulide, tolazamide, tolbutamide, tolmentin and zomepirac.
5. A composition according to claim 1, wherein the therapeutically active moiety is preferably selected from hypoglycemic agent and anti-inflammatory agent.
6. A composition according to claim 5, wherein the hypoglycemic agent used is selected from the category of sulfonylurea.
7. A composition according to claim 6, wherein the sulfonylurea used is selected from the group consisting of glipizide, glimepiride, and glyburide.
8. A composition according to claim 5, wherein the anti-inflammatory agent is selected from the group consisting of aspirin, paracetamol, ibuprofen, indomethacin, ketoprofen, naproxen, nimesulide, tolmentin and zomepirac preferably selected from Aspirin.
9. A composition according to claim 1, wherein the dose of the therapeutically active moiety per tablet ranges between 0.1 mg to 600 mg.
10. A composition according to claim 1, wherein the alkalinizing agent or the buffer used is soluble in water and improves the solubility of therapeutically active moiety in the aqueous fluids by increasing the micro environmental pH of the core above the pKa value of the therapeutically active moiety.
11. A composition according to claim 10, wherein the alkalinizing agent used is selected from the group consisting of sodium bicarbonate, potassium bicarbonate, sodium citrate, potassium citrate, tris(hydroxymethyl)aminomethane, meglumine, and/or the mixture thereof.
12. A composition according to claim 10, wherein the buffer used is selected from the group consisting of sodium phosphates, potassium phosphates, sodium citrate, potassium citrate, sodium acetate, tris(hydroxymethyl)aminomethane, and/or mixtures thereof.
13. A composition according to claim 1, wherein the ratio of the therapeutically active ingredient to the alkalinizing agent is in the range of 0.1:9.9 to 7:3.
14. A composition according to claim 1, wherein the ratio of the therapeutically active ingredient to the buffer is in the range of 0.1:9.9 to 7:3.

15. A composition according to claim 1, wherein the osmotically effective solute used is selected from the group consisting of sodium chloride, potassium chloride, mannitol, sorbitol, and carbohydrates selected from the group consisting of sucrose, glucose, fructose, dextrose, lactose, and mixtures of above said osmagents.
- 5 16. A composition according to claim 15, wherein the osmotically effective solute used is preferably selected from the group consisting of sodium chloride, mannitol, and lactose.
17. A composition according to claim 1, wherein the core components exerts osmotic gradient across the wall of release rate controlling membrane against the external fluids.
- 10 18. A composition according to claim 1, wherein the semi permeable membrane forming polymer is water insoluble, which allows water to permeate and substantially prevents permeability of compositions of the tablet core.
19. A composition according to claim 1, wherein the semi-permeable membrane forming polymer is selected from group consisting of cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, polymers of acrylic and methacrylic acid and esters thereof.
- 15 20. A composition according to claim 19, wherein the preferred semi-permeable membrane forming polymer is selected from cellulose acetate and ethyl cellulose.
- 20 21. A composition according to claim 1, wherein the permeable membrane forming is a water-soluble, which allows water to permeate along with at least one of the components of the core.
22. A composition according to claim 1, wherein the permeable membrane forming polymer is selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, cellulose ethers, polyethylene glycols, polymers of acrylic and methacrylic acid and esters thereof.
- 25 23. A composition according to claim 22, wherein the preferred permeable membrane forming polymer used is selected from polyvinyl pyrrolidone and hydroxypropylmethyl cellulose.
- 30 24. A composition according to claim 1, wherein the ratio of semi-permeable water insoluble polymer membrane to permeable water soluble polymer membrane is in the range of 9:1 to 1:9, preferably in the range of 9:1 to 3:7.
25. A composition according to claim 1, wherein the plasticizer used is having controlled solubility in water.

26. A composition according to claim 25, wherein the plasticizer used is selected from the group consisting of dibutyl sebacate, diethyl phthalate, dibutyl phthalate, triacetin, triethyl citrate, tributyl citrate, castor oil, propylene glycol, glycerol, polyethylene glycols, liquid sorbitol, and/or mixture thereof.
- 5 27. A composition according to claim 1, wherein by adjusting the polymer forming membrane weight coated on the tablet core, thickness of the membrane wall is controlled.
28. A composition according to claim 1, wherein the thickness of the membrane wall ranges between 1 to 1000 microns
- 10 29. A composition according to claim 28, wherein the preferred thickness of the membrane wall ranges between 50 to 500 microns
30. A composition according to claim 1, wherein the pharmaceutically acceptable excipient used is (are) selected from the group consisting of magnesium stearate, talc and aerosil.
- 15 31. A composition according to claim 1, from wherein the mechanism of release of the therapeutically active ingredient is based on combination of osmotic pumping and diffusion.
32. A process for the preparation of pharmaceutical composition as claimed in claim 1 for sustained release of a therapeutically active moiety, said process comprising:
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- a. preparing a core composition by dry blending a therapeutically active moiety, an alkalinizing agent or a buffer compound, an osmotically effective solute and optionally containing one or more pharmaceutically acceptable excipients and polymers, or
- 25 b. preparing the core composition by slugging or wet granulation techniques by blending the drug with the other excipients including alkalinizing agent(s)/buffer(s) and osmagent using water, alcohol, or an organic co solvent such as isopropyl alcohol/methylene chloride, in the ratio 80/20, V/V as the granulation fluid to obtain wet granules, or
- 30 c. by dissolving the drug and the solubility modifier in a common aqueous or organic solvent and after evaporation to dryness, mixing the residue with osmagent and other excipients needed to obtain core composition,
- d. compressing the above core composition obtained in steps (a), (b) and (c) to obtain tablets core by using conventional tablet making machine,

- e. preparing coating solution by dissolving required amount of semi permeable membrane forming polymer in a solvent selected from methylene chloride, methanol, ethanol or mixture thereof,
- f. adding permeable membrane forming polymer and one or more plasticizer to the solution of step (e) with continuous stirring,
- 5 g. coating the compressed tablet of step (d) with the coating solution of step (f) by using the techniques selected from press coating, spraying, dipping, or air suspension techniques and
- h. drying the coated tablet core obtained in the step (g) at 45-60°C for about 16
- 10 hours to obtain the composition for sustained release and packing the tablets by conventional methods.
33. The process according to claim 32 wherein in step (a), the mixture obtained by dry blending is passed through standard sieves to obtain uniform particle size so as to form core composition
- 15 34. The process according to claim 32 wherein in step (b), the wet granules are dried at a temperature ranging between 40 and 60°C for about 10 minutes, passing the granules through 20-22 standard sieves to break agglomerates and to making it uniform particle size to obtain core composition.
- 20 35. The process according to claim 32, wherein the therapeutically active moiety is selected from a group consisting of acetazolamide, acetyl salicylic acid, p-amino salicylic acid, captopril, carbenicillin, carbenoxolone, chlorpropamide, clofibrate, diclofenac, diflunisal, ethacrynic acid, etodolac, fenoprofen, furosemide, gliclazide, glimepiride, glipizide, glyburide, ibuprofen, indomethacin, ketoprofen, naproxen, nimesulide, tolazamide, tolbutamide, tolmentin and zomepirac.
- 25 36. The process according to claim 32, wherein the therapeutically active moiety is preferably selected from hypoglycemic agent and anti-inflammatory agent.
37. The process according to claim 36, wherein the hypoglycemic agent used is selected from the category of sulfonylurea.
38. The process according to claim 37, wherein the sulfonylurea used is selected from
- 30 the group consisting of glipizide, gliclazide, glimepiride, and glyburide.
39. The process according to claim 36, wherein the anti-inflammatory agent is selected from group consisting of aspirin, paracetamol, ibuprofen, indomethacin, ketoprofen, naproxen, nimesulide, tolmentin and zomepirac preferably selected from Asprin.

40. The process according to claim 32, wherein the dose of the therapeutically active moiety per tablet ranges between 0.1 mg to 600 mg.
41. The process according to claim 32, wherein the alkalinizing agent used is selected from the group consisting of sodium bicarbonate, potassium bicarbonate, sodium citrate, potassium citrate, tris(hydroxymethyl)aminomethane, meglumine, and/or the mixture thereof.
42. The process according to claim 32, wherein the buffer used is selected from the group consisting of sodium phosphates, potassium phosphates, sodium citrate, potassium citrate, sodium acetate, tris(hydroxymethyl)aminomethane, and/or mixtures thereof.
43. The process according to claim 32, wherein the ratio of the therapeutically active ingredient to the alkalinizing agent is in the range of 0.1:9.9 to 7:3.
44. The process according to claim 32, wherein the ratio of the therapeutically active ingredient to the buffer is in the range of 0.1:9.9 to 7:3.
45. The process according to claim 32, wherein the osmotically effective solute used is selected from the group consisting of sodium chloride, potassium chloride, mannitol, sorbitol, and carbohydrates selected from the group consisting of sucrose, glucose, fructose, dextrose, lactose, and mixture thereof.
46. The process according to claim 45, wherein the osmotically effective solute used is preferably selected from the group consisting of sodium chloride, mannitol, and lactose.
47. The process according to claim 32, wherein the excipient(s) used is(are) selected from group consisting of magnesium stearate, talc and aerosil.
48. The process according to claim 32, wherein the polymer(s) used is(are) selected from group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, cellulose ethers, polyethylene glycols, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose polymers of acrylic and methacrylic acid and esters thereof.
49. The process according to claim 32, wherein the semi-permeable membrane forming polymer is selected from group consisting of cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, ethyl cellulose, polymers of acrylic and methacrylic acid and esters thereof.
50. The process according to claim 49, wherein the preferred semi-permeable membrane forming polymer is selected from cellulose acetate and ethyl cellulose.

51. The process according to claim 32, wherein the permeable membrane forming polymer is selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidone, cellulose ethers, polyethylene glycols, polymers of acrylic and methacrylic acid and esters thereof.
- 5 52. The process according to claim 51, wherein the preferred the permeable membrane forming polymer used is selected from polyvinyl pyrrolidone and hydroxypropylmethyl cellulose.
53. The process according to claim 32, wherein the ratio of semi-permeable water insoluble polymer membrane to permeable water soluble polymer membrane is in the range of 9:1 to 1:9, preferably in the range of 9:1 to 3:7.
- 10 54. The process according to claim 32, wherein by adjusting the polymer forming membrane weight coated on the tablet core, thickness of the membrane wall is controlled.
55. The process according to claim 32, wherein the weight of coating solution on the tablet core is up to 20% by weight of tablet core.
- 15 56. The process according to claim 32, wherein the thickness of the membrane wall ranges between 1 to 1000 microns, preferably between 50 to 500 microns.
57. The process according to claim 32, wherein the plasticizer used is selected from the group consisting of dibutyl sebacate, diethyl phthalate, dibutyl phthalate, triacetin, triethyl citrate, tributyl citrate, castor oil, propylene glycol, glycerol, polyethylene glycols, liquid sorbitol, and/or mixture thereof.
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United States Patent [19]

Loew et al.

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[54] IBUPROFEN-CONTAINING MEDICAMENT

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[21] Appl. No.: 119,028

[22] Filed: Nov. 10, 1987

[30] Foreign Application Priority Data

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[52] U.S. Cl. 424/451; 424/456; 424/468; 514/557

[58] Field of Search 514/557; 424/488, 454, 424/456, 457, 451, 463

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Primary Examiner—Nancy A. B. Swisher
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[57] ABSTRACT

An ibuprofen-containing medicament which contains ibuprofen only in the (S)-(+)-form is disclosed. (S)-(+)-ibuprofen is more than twice as active as the racemate which has until now been used in the treatment of rheumatism. This permits reduction of the quantity of active ingredient and the size of the tablets or dragees.

6 Claims, No Drawings

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after this time period are equally high or higher levels achieved after administration of the (R)-(-)-form than after administration of the (S)-(+)-form. Since these levels are less than 10% of the maximum level they no longer contribute to the required activity.

Thus it can also be explained from a pharmacokinetic point of view that within the known period of action of ibuprofen (ca. 6 hours) no effect can be expected from the (R)-(-)-form.

We claim:

1. An ibuprofen containing medicament containing only ibuprofen in the (S)-(-)- form without any ibuprofen in the (R)-(-)- form, the medicament being in sustained release form in association with a pharmaceutically acceptable carrier.

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2. Medicament according to claim 1 wherein the ibuprofen containing medicament is in the form of a preparation suitable for oral administration.

3. Medicament according to claim 1 wherein the ibuprofen containing medicament is in the form of a preparation suitable for rectal administration.

4. Ibuprofen containing medicament according to claim 1 containing (S)-(-)-ibuprofen in sustained-release form in combination with (S)-(-)-ibuprofen in non-sustained-release form.

5. Ibuprofen containing a medicament according to claim 1 wherein the medicament is in form of a capsule.

6. Ibuprofen containing a medicament according to claim 1 containing said (S)-(-)-ibuprofen in combination with an amino acid.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/DK98/00388 (22) International Filing Date: 10 September 1998 (10.09.98) (30) Priority Data: 1044/97 11 September 1997 (11.09.97) DK (71) Applicant (for all designated States except US): NYCOMED DANMARK A/S [DK/DK]; Langebjerg 1, Postboks 88, DK-4000 Roskilde (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): SKINHØJ, Annette [DK/DK]; Moseholmene 3B, DK-2610 Rødovre (DK). BERTELSEN, Poul [DK/DK]; Duevej 42, 4. th., DK-2000 Frederiksberg (DK). (74) Agent: PLOUGMANN, VINGTOFT & PARTNERS A/S; Sankt Annæ Plads 11, Postboks 3007, DK-1021 København (DK).		(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: MODIFIED RELEASE MULTIPLE-UNITS COMPOSITIONS OF NON-STEROID ANTI-INFLAMMATORY DRUG SUBSTANCES (NSAIDs) (57) Abstract An oral pharmaceutical modified release multiple-units composition for the administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (in the following abbreviated "an NSAID substance") to obtain both a relatively fast or quick onset of the therapeutic effect and the maintenance of a therapeutically active plasma concentration for a relatively long period of time. The modified release multiple-units composition comprises at least two fractions of multiple units such as a first and a second fraction. The first fraction comprises individual units which are designed to quickly release the drug substance and the second fraction comprises individual units which are designed to slowly release the drug substance to enable a delayed and extended release of the drug substance. Typically, the second fraction comprises multiple units which are coated with a sustained release coating designed to release the drug substance in such a manner that the maintenance of a therapeutically active plasma concentration for a relatively long period of time are obtained. By suitable adjustment of the release pattern of the at least first and second fraction a composition is obtained which is adapted to once- or twice-a-day administration.		

CLAIMS

1. An oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising at least two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, and

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ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test,

the second fraction being in the form of coated delayed release multiple units for extended release of the NSAID substance.

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2. A composition according to claim 1, wherein the first fraction - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w or at least about 80% w/w of the total NSAID substance present in the first fraction within the first 20 min of the test.

3. A composition according to claim 1 or 2, wherein the quick *in vitro* release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at the most 15% w/w such as at the most 10% w/w or at the most 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III defined herein.

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4. A composition according to any one of the preceding claims, wherein the NSAID substance contained in the first fraction has a pK_a value between from about 3.0 to about 5.5 and the first fraction is in the form of uncoated units.
- 5 5. A composition according to any one of the preceding claims, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at the most about 0.5% w/v such as, e.g. at the most about 0.1% w/v, at the most about 0.05% w/v, at the most about 0.03% w/v, at the most about 0.01% w/w, at the most about 0.007% w/v, at the most about 0.005% w/v, at the most about 0.003% w/v, at the
10 most about 0.002% w/v or at the most about 0.001% w/v.
6. A composition according to any one of claims 1-3, wherein the NSAID substance contained in the first fraction has a pK_a value of at least 5.0 such as at least about 5.5.
- 15 7. A composition according to claim 6, wherein the first fraction is present in the form of coated units.
8. A composition according to any one of claims 1-3 or 6-7, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at least
20 about 0.1% w/v such as e.g. at least about 0.5% w/v or at least about 1% w/v.
9. A composition according to any one of the preceding claims intended for administration once or twice daily.
- 25 10. A composition according to any one of the preceding claims for the administration of a therapeutically and/or prophylactically effective amount of an NSAID substance to obtain both a relatively fast onset of the therapeutic effect and the maintenance of therapeutically active plasma concentration for a relatively long period of time, a unit dosage of the composition comprising at least two fractions as follows:
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- a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration in order to enable dosing once or twice daily,

- 5 the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick
10 release multiple-units, as measured by the dissolution method II as defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by e.g. the dissolution method III as defined herein,

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the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at least about 15% w/w such as, e.g., at least about
20 10% w/w or at least about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III defined herein.

11. A composition according to any one of the preceding claims, wherein the NSAID substance is selected from the group consisting of lornoxicam, diclofenac, nimesulide,
25 ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acetaminophen, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen, and pharmaceutically acceptable salts, complexes and/or prodrugs thereof
30 and mixtures thereof.

12. A composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is the same as the NSAID substance contained in the second fraction.

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13. A composition according to any one claims 1-11, wherein the NSAID substance in the first fraction is different from the NSAID substance contained in the second fraction.
14. A composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is lornoxicam.
15. A composition according to any one of the preceding claims, wherein the NSAID substance in the second fraction is lornoxicam.
- 10 16. A composition according to any one of the preceding claims comprising a further active drug substance.
17. A composition according to any one of the preceding claims, wherein a further active drug substance is included in at least one of the first and second fraction.
- 15 18. A composition according to claim 16 or 17, wherein the further active drug substance is an antidepressant, an opioid, a prostaglandine analog (e.g. misoprostol), a glucocorticosteroid, a cytostaticum (e.g. methotrexate), a H₂ receptor antagonist (e.g. cimetidine, ranitidine), a proton pump inhibitor (e.g. pantoprazole, omeprazole, lansoprazole) and/or an antacidum.
- 20 19. A composition according to claim 16 or 17, wherein the further active drug substance is paracetamol, penicillamine, sulfasalazine and/or auranorfin.
- 25 20. A composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam.
21. A composition according to any one of the preceding claims, wherein the quick release multiple-units of the first fraction have a mean particle size of at the most about 250 µm such as, e.g. at the most about 240 µm, at the most about 230 µm, at the most about 220 µm, at the most about 210 µm, at the most about 200 µm, at the most about 190 µm, at the most about 180 µm, at the most about 175 µm, at the most about 150 µm, at the most about 125 µm, at the most about 100 µm, at the most about 90 µm or at the most about 80 µm.

22. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple-units provides within 1 hour a release as defined by the dissolution method II defined herein of at least 50% w/w, such as, e.g., at least about 60% w/w, at least about 70% w/w, at at least
5 about 80% w/w, at least about 85% w/w at least about 90% w/w or at least about 95% w/w of the NSAID substance.

23. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units
10 provides within 1 hour a release as defined by the dissolution method III defined herein in the range of 0%-30% w/w, such as in the range of 0%-20% w/w, in the range of 0%-10% w/w, such as at the most about 5% w/w of the NSAID substance.

24. A composition according to any one of the preceding claims, wherein the *in vitro*
15 dissolution characteristics of the second fraction of extended release multiple-units provides within 3 hours a release as defined by the dissolution method III defined herein in the range of about 10%-70% w/w, such as, e.g., in the range of about 10%-60% w/w, in the range of about 12%-50% w/w, in the range of 14%-45% w/w, in the range of about 15%-30% w/w, in the range of about 15%-20% w/w such as, e.g., about
20 17% w/w of the NSAID substance.

25. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 6 hours a release as defined by the dissolution method III defined herein
25 in the range of about 35%-95% w/w, such as, e.g., in the range of about 50%-90% w/w, in the range of about 50%-80% w/w, in the range of 50%-75% w/w, in the range of about 50%-60% w/w, in the range of about 53%-59% w/w such as, e.g. about 56% w/w of the NSAID substance.

30 26. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of modified release multiple-units provides within 9 hours a release as defined by the dissolution method III defined herein in the range of about 50%-100% w/w, such as, e.g., in the range of about 60%-98% w/w, in the range of about 65%-95% w/w, in the range of about 70%-90% w/w, in the
35 range of about 70%-80% w/w such as, e.g., about 76% w/w of the NSAID substance.

27. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first and second fractions are adapted so that the first fraction is substantially released when the release from the second fraction is initiated
5 corresponding to at least 50% w/w of the first fraction at the time at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the second fraction is released as measured by the dissolution method III defined herein.
28. A composition according to any one of the preceding claims, wherein the *in vitro*
10 dissolution characteristics of the first and second fractions are adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 70% w/w release of the first fraction at the time at the most about 20% w/w such as, e.g. at the most about 15% or at the most about 10% w/w of the second fraction is released as measured by the dissolution method III as defined
15 herein.
29. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 1 hour a release of the NSAID substance from the composition in the range of about 5-50% w/w, such as,
20 e.g., in the range of about 5-45% w/w, in the range of about 15-40% w/w, in the range of about 20-35% w/w such as about 29% w/w, as defined by the dissolution method III as defined herein.
30. A composition according to any one of the preceding claims, wherein the *in vitro*
25 dissolution characteristics of the composition provides within 3 hours a release as defined by the dissolution method III as defined herein in the range of about 20-80% w/w, such as, e.g., in the range of about 25-70% w/w, in the range of about 30-60% w/w, in the range of about 35-55% w/w such as about 42% w/w.
- 30 31. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 6 hours a release as defined by the dissolution method III defined herein in the range of about 40-98% w/w, such as, e.g., in the range of about 50-95% w/w, in the range of about 60-90% w/w, in the range of about 60-85% w/w, most preferred in the range of about 60-83% w/w
35 such as about 69% w/w.

32. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 9 hours a release as defined by the dissolution method III as defined herein in the range of about 50-100%
5 w/w, such as, e.g., in the range of about 60-99% w/w, in the range of about 70-98% w/w, in the range of about 70-97% w/w, in the range of about 75-96% w/w, in the range of about 80-96% w/w, about 80-85% w/w such as about 83% w/w.

33. A composition according to any one of the preceding claims, wherein the
10 percentage of NSAID substance in the first fraction is in the range of about 5%-50% w/w such as, e.g., in the range of about 10%-45% w/w, in the range of about 15%-45% w/w, in the range of about 20%-40% w/w, in the range of about 25%-40% w/w, in the range of about 25%-35% w/w such as, e.g., about 30% w/w, calculated on the total amount of NSAID substance in the composition.

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34. A composition according to any one of the preceding claims, wherein the percentage of NSAID substance in the second fraction is in the range of about 30%-99% w/w such as, e.g. in the range of about 40%-98% w/w, in the range of about 45%-95% w/w, in the range of about 50%-95% w/w, in the range of about 55%-85%
20 w/w, in the range of about 60%-80% w/w, in the range of about 60%-75% w/w, in the range of about 65%-75% w/w such as, e.g., about 70% w/w, calculated on the total amount of NSAID substance in the composition.

35. A composition according to any one of the preceding claims, wherein the multiple-
25 units of the second fraction are coated cross-sectionally substantially homogeneous pellets.

36. A composition according to any one of the preceding claims, wherein the multiple-units of the first fraction are cross-sectionally substantially homogeneous pellets.

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37. A composition according to any one of the preceding claims, wherein the first fraction results in a peak plasma concentration of NSAID substance which is substantially the same as the peak plasma concentration resulting from the second fraction.

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38. A composition according to any one of claims 1-36, wherein the first fraction results in a peak plasma concentration of the NSAID substance which is higher than the peak plasma concentration resulting from the second fraction.
- 5 39. A composition according to any one of claims 1-36, wherein the first fraction results in a peak plasma concentration of the NSAID substance which is lower than the peak plasma concentration resulting from the second fraction.
40. A composition according to any one of the preceding claims, wherein the first
10 fraction results in a therapeutically active plasma concentration of the NSAID substance until the extended release of an NSAID substance from the second fraction of modified release multiple-units contributes to the maintenance of a therapeutically active plasma concentration of the NSAID substance.
- 15 41. A composition according to any one of the preceding claims, wherein the extended release coating of the second fraction is substantially water-insoluble, but water-diffusible and substantially pH-independent.
42. A composition according to any one of the preceding claims, wherein the first
20 fraction is coated units and the coating is a substantially water-insoluble, but water-diffusible and substantially pH-independent coating.
43. A composition according to any one of the preceding claims, wherein a unit dosage of the composition comprises from about 1 to about 32 mg of the NSAID substance.
- 25 44. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 1 mg to about 1.6 g such as from about 1 mg to about 1.2 g of the NSAID substance.
- 30 45. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 50 mg to about 1.1 g of the NSAID substance.
46. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 100 mg to about 1.0 g of the NSAID substance.

47. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 200 mg to about 900 mg of the NSAID substance.
48. A composition according to any one of claims 1-42, wherein a unit dosage
5 comprises from about 300 mg to about 800 mg of the NSAID substance.
49. A composition according to any one of the preceding claims comprising a unit dosage for the administration of the therapeutically effective amount of the NSAID substance twice daily.
- 10 50. A composition according to any one of claims 1-48 comprising a unit dosage for the administration of the therapeutically effective amount of the NSAID substance once daily.
- 15 51. A composition according to any one of the preceding claims wherein the unit dosage of the composition is in the form of a capsule, tablet or sachet.
52. A composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam and the unit dosage of the composition contains 4, 8, 12, 16,
20 20, 24, 28, 32 or 36 mg of lornoxicam.
53. A process for the preparation of a unit dosage form of an oral pharmaceutical modified release composition according to any one of the preceding claims, the process comprising incorporating into the unit dosage form at least two fractions as follows:
25 a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically or prophylactically active plasma concentration within a relatively short period of time, and a second fraction of coated extended release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically active plasma concentration in order to enable dosing once or
30 twice daily,
- the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

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a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of

- 5 extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein, the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least about 50% w/w release of the NSAID substance contained in
- 10 the first fraction at the time when at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

- 15 54. A method for treating a patient suffering from pain and/or inflammatory conditions and/or the like comprising administering to the patient an effective amount of an NSAID substance in the form of a composition according to any one of claims 1-52 once or twice daily.
- 20 55. A method for administering a therapeutically and/or prophylactically effective amount of an NSAID substance to a patient in need thereof to obtain both a relatively fast onset of the therapeutic effect and the maintenance of therapeutically active plasma concentration for a relatively long period of time, the method comprising administering once or twice daily a unit dosage of a composition comprising at least two
- 25 fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

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a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration.

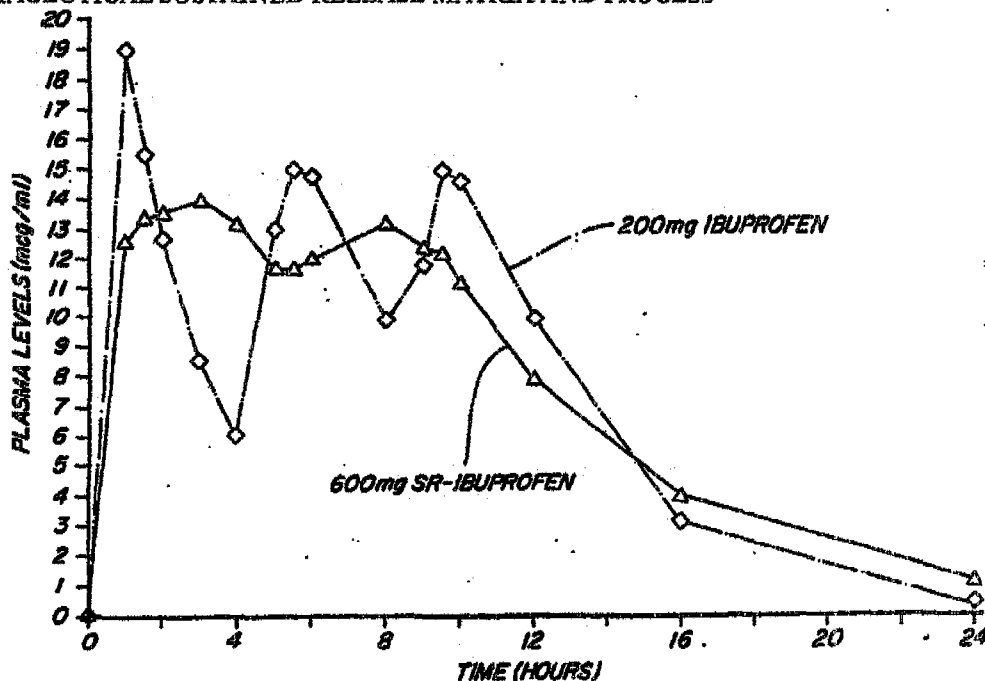
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(54) Title: PHARMACEUTICAL SUSTAINED RELEASE MATRIX AND PROCESS



(57) Abstract

A pharmaceutical sustained release homogeneous tablet or homogeneous tablet layer is formed by making a wet granulation using povidone (PVP) in alcohol as the granulating fluid which is mixed with a pharmaceutical active, ethylcellulose, a wicking agent, e.g. microcrystalline cellulose, an erosion promoter, e.g. pregelatinized starch, then drying and milling the granulation and blending with a dry powdered erosion promoter, wicking agent, lubricant, e.g. magnesium stearate and glidant, e.g. silicon dioxide, and compressing the resultant granulation, which upon administration results in a long-lasting slow and relatively regular incremental release of the pharmaceutical active, and multi-layered pharmaceutical active tablets comprising immediate release and/or sustained release layers.

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209What Is Claimed Is:

1. A process of preparing a pharmaceutical active sustained release shaped and compressed homogeneous tablet or tablet layer characterized by a long-lasting slow and relatively regular incremental release of the pharmaceutical active upon administration comprising the following steps:
- A) forming a granulating agent by dissolving 5-30 parts, by weight of total non-active components of the tablet, of povidone in alcohol or an alcohol-water mixture;
- B) blending together the following ingredients in dry powder form: an effective amount of pharmaceutical active which is sufficient to comprise about 66 to 96 percent by weight of the total tablet composition; and the following range of amounts of non-active ingredients given in a range of parts by weight of the total non-active components of the tablet;
- | | <u>Ingredient</u> | <u>Parts by Weight</u> |
|------------------|-------------------|------------------------|
| ethylcellulose | 3-12 | |
| wicking agent | 10-35 | |
| erosion promoter | 5-25 | |
- C) adding the granulating agent from Step A to the blended powders from Step B, and forming a wet granulation;
- D) drying the wet granulation of Step C;
- E) milling the dried granulation from Step D;

F) thoroughly blending the milled dried granulation from Step E with the following ingredients in dry powder form:

5	<u>Ingredient</u>	<u>Parts by Weight</u>
	erosion Promoter	1-20
	wicking agent	3-20
	lubricant	0-10
	glidant	0-10; and

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G) compressing the final granulation from Step F into a tablet or tablet layer wherein the active to non-active component ratio is at least about 2:1.

15 2. The process of claim 1 wherein:

in Step A the alcohol used is selected from the group consisting of alcohol USP, dehydrated alcohol USP, and methyl alcohol USP, and isopropyl alcohol USP;

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in Step B the wicking agent used is microcrystalline cellulose or powdered cellulose and the erosion promoter used is pregelatinized starch or starch NF or rice starch; and

25

in Step C the wet granulation is formed by mixing in a high shear granulator; and

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in Step F the erosion promoter used is 3-20 parts by weight of either pregelatinized starch or starch NF or rice starch or is 1-15 Parts by weight of sodium starch glycolate or croscarmellose sodium or crospovidone; the lubricant used is magnesium stearate or stearic acid; and, the glidant used is colloidal silicon dioxide or fumed silicon dioxide.

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3. The process of claim 2 wherein:
in Step A the alcohol used is alcohol USP;

5 in Step B the wicking agent used is microcrystalline
cellulose, the erosion promoter used is pregelatinized
starch; in Step F the erosion promoter used is
pregelatinized starch; in Step F the erosion promoter
used is pregelatinized starch; the lubricant used is
10 magnesium stearate; and the glidant used is colloidal
silicon dioxide.

4. The process of claim 3 wherein the specific
ingredients and amounts used are:

15	<u>Step</u>	<u>Ingredient</u>	<u>Parts by Weight</u>
	A	alcohol-water (1:1)	q.s.
		Povidone	14.7
	B	Pharmaceutical Active	170-2000
20		Ethylcellulose	7.3
		Microcrystalline Cellulose	22
		Pregelatinized Starch	14
	F	Pregelatinized Starch	8
		Microcrystalline Cellulose	7.3
25		Magnesium Stearate	5
		Colloidal Silicon Dioxide	5

5. The process of claim 1 wherein the pharmaceutical
active is selected from the group consisting of
30 analgesics, antiarthritics, antiasthmatics,
antidepressants, appetite suppressants, antihistamines,
antibiotics, antipsychotics, anti-ulcers, anti-
inflammatories, antitussives, antianginals, decongestants
and combinations thereof.

active is selected from the group consisting of codeine, amitriptyline, phenylpropanolamine, chlorpheniramine maleate, naproxen, indomethacin, ampicillin, thioridazine, cimetidine, theophylline, aminophylline, isosorbide dinitrate, tolmetin, pseudoephedrine, destromethorphan, ibuprofen and caffeine, and other combinations thereof.

7. The process of claim 1 wherein at least one additional layer comprising a pharmaceutical active ingredient is combined with the homogeneous sustained release composition to produce a shaped and compressed multilayer tablet.

8. A shaped and compressed sustained release therapeutic composition comprising an effective amount of a pharmaceutical active and a granulating agent and excipients combined into a matrix, characterized by a long-lasting slow and relatively regular incremental release of the pharmaceutical active upon administration, wherein the granulating agent and excipients includes a combination of two polymers, ethylcellulose and povidone, wherein the total amount of granulating agent and excipients is an amount effective to form a solid matrix of active and binder materials and is less than 33 percent of the weight of said shaped and compressed composition.

9. The composition of claim 8 wherein the total amount of granulating agent and excipients is less than 20 percent of the weight of said shaped and compressed composition.

10. The composition of claim 8 wherein the total amount of granulating agent and excipients is in the range of 10 to 20 percent of the weight of said shaped and compressed composition.

11. The composition of claim 8 wherein the total amount of

11. The composition of claim 8 wherein the total amount of granulating agent and excipients is in the range of 5 to 33 percent of the weight of said shaped and compressed composition.

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12. A shaped and compressed pharmaceutical active sustained release tablet made by wet granulating a pharmaceutical active and the Excipients of Part I with the Granulating Agent of Part II, drying and milling the resultant granulations, and then blending with the
10 Excipients of Part III and compressing into a tablet, wherein the pharmaceutical active is added in Part I and comprises at least 66% of the total weight of the tablet and the inactive ingredients of Parts I, II and III
15 comprise the following:

	<u>Ingredient</u>	<u>Parts by</u> <u>Weight Range of</u> <u>total Inactive</u> <u>Ingredients</u>
20	Part I <u>Excipients</u>	
	Ethyl Cellulose	3 - 12
	Microcrystalline Cellulose	10 - 35
25	Pregelatinized Starch	5 - 25
	Part II <u>Granulating Agent</u>	
	Povidone	5 - 30
	Alcohol or Alcohol-Water	
30	Part III <u>Excipients</u>	
	Pregelatinized Starch	3 - 20
	Microcrystalline Cellulose	2 - 10
	Magnesium Stearate	2 - 10
35	Colloidal Silicon Dioxide	2 - 10

13. A shaped and compressed bi-layer immediate release and sustained release therapeutic composition comprising a pharmaceutical active in both layers wherein the immediate release layer comprises a pharmaceutical active and pharmaceutically acceptable excipients and the sustained release layer comprises a granulating agent and excipients combined into a matrix, characterized by a long-lasting slow and relatively regular incremental release of a pharmaceutical active upon administration, wherein the granulating agent and excipients includes a combination of two polymers, ethylcellulose and povidone, and wherein the total amount of granulating agent and excipients is less than 33 percent of the weight of the sustained release layer of said shaped and compressed bi-layer composition.

14. The therapeutic composition of claim 13 wherein the immediate release layer comprises a pharmaceutical active; microcrystalline cellulose; starch; sodium starch glycolate; and a granulating agent.

15. The bi-layered therapeutic composition of claim 14 wherein the pharmaceutical active in both layers is the same or different and is selected from the group consisting of analgesics, antiarthritics, antiasthmatics, antidepressants, appetite suppressants, antihistamines, antibiotics, antipsychotics, anti-ulcers, anti-inflammatory, antitussives, antiaginals, decongestants and combinations thereof.

16. A shaped and compressed bi-layer composition according to claim 13 wherein the pharmaceutical active in both layers is the same.

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17. A shaped and compressed multilayered therapeutic composition comprising at least two layers of a sustained release composition according to claim 13 wherein the pharmaceutical actives of each layer are different.

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18. A shaped and compressed bi-layered immediate release and sustained release pharmaceutical active tablet made by combining an immediate release layer comprising a pharmaceutical active and pharmaceutically acceptable excipients with a sustained release layer made by wet granulating the Active & Excipients ingredients of Part II, drying and milling the resultant granulations, and then blending with the Excipients of Part III and compressing the two layers into a tablet, wherein the ingredients of Parts I, II and III comprise the following:

	<u>Ingredient</u>	<u>Range of Parts by Weight</u>
20	Part I <u>Active & Excipients</u>	
	Pharmaceutical Active	170-2000
	Ethyl Cellulose	3 - 12
	Microcrystalline Cellulose	10 - 35
	Pregelatinized Starch	5 - 25
25	Part II <u>Granulating Agent</u>	
	Povidone	5 - 30
	Alcohol or Alcohol-Water	q.t.
30	Part III <u>Excipients</u>	
	Pregelatinized Starch	3 - 20
	Microcrystalline Cellulose	2 - 10
	Magnesium Stearate	2 - 10
	Colloidal Silicon Dioxide	2 - 10

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19. A multilayered composition according to claim 17
comprising at least one additional of an immediate release
composition comprising a pharmaceutical active wherein the
pharmaceutical active is the same or different as the
5 pharmaceutical active comprising the sustained release
layers.

20. A bi-layered tablet according to claim 18 wherein at
least one layer comprises caffeine.

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Therapeutic agents.

Sustained release granules of ibuprofen comprising a homogeneous mixture of ibuprofen and a pharmaceutically acceptable polymeric material, operable to provide a slow release of ibuprofen over a pH range from 1.0 to 7.0, the polymeric material being present in an amount of 5% to 25% by weight, based on the weight of the ibuprofen. The granules are prepared by dissolving the ibuprofen and polymeric material in a solvent and evaporating the solvent. Suitable polymeric materials include ethyl cellulose, high viscosity hydroxy propyl methyl cellulose and copolymers of dimethyl aminoethyl methacrylate and methacrylic acid ester. The granules may be compressed to form sustained release tablets.

noticeable advantage arises from the coprecipitated granules of the present invention.

The rate of dissolution of the tablets of Examples 8, 2, 4a, 3a and 6 was determined in comparison with that of conventional tablets. A modified dissolution method with 50 RPM of Apparatus II for ibuprofen tablets (USP XXI, page 527) was used. A 10 ml sample was pipetted out of the dissolution medium at hourly time periods (except for conventional release tablets) and replaced by the same quantity of $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$ pH 7.2 buffer solution. The filtrate of the sample was assayed by a spectrophotometer at 265 nm and the released amount of ibuprofen was calculated as a percentage of the total content.

These results show that the release rate of drug from tablets made with co-crystallisation granules of the invention can range from slow (Example 6) to fast (Example 8) in a predetermined manner. By adjusting the combination of the different type, viscosity and concentration of polymers in the granules of the present invention, a desirable controlled release dosage form can be prepared.

15 Claims

1. A sustained release pharmaceutical composition which comprises granules comprising a homogeneous mixture of ibuprofen and a pharmaceutically acceptable polymeric material operable to provide a slow release of ibuprofen over a pH range from 1.0 to 7.5, the polymeric material being present in an amount of 5% to 25% by weight, based on the weight of the ibuprofen.
2. A pharmaceutical composition according to claim 1 in which the polymeric material is present in an amount of 5% to 15% by weight, based on the weight of the ibuprofen.
3. A pharmaceutical composition according to claim 1 or claim 2 in which the polymeric material comprises ethyl cellulose, a copolymer of dimethylaminoethyl methacrylate and methacrylic acid ester or high viscosity hydroxy propyl methyl cellulose.
4. A pharmaceutical composition according to claim 3 in which the polymeric material comprises ethyl cellulose.
5. A pharmaceutical composition according to any one of claims 1 to 4 in the form of a tablet comprising said granules.
6. A tablet which comprises granules comprising a homogeneous mixture of ibuprofen and ethyl cellulose, the ethyl cellulose being present in an amount of 5% to 15% by weight, based on the weight of ibuprofen.
7. A tablet according to claim 6 in which the ethyl cellulose is present in an amount of 10% by weight, based on the weight of ibuprofen.
8. A tablet according to claim 6 or claim 7 also comprising a disintegrating agent.
9. A process for the preparation of sustained release granules comprising ibuprofen and a pharmaceutically acceptable polymeric material operable to provide a slow release of the ibuprofen over the pH range 1.0 to 7.5, the polymeric material being present in an amount of 5% to 25% by weight, based on the weight of ibuprofen, which comprises dissolving the ibuprofen and the polymeric material in a solvent and evaporating the solvent to form granules of coprecipitated ibuprofen and polymeric material.
10. A process according to claim 9 for the production of granules according to any one of claims 1 to 4.
11. A process for the production of tablets which comprises the compression of granules prepared by the process of claim 10.
12. A process according to claim 11 for the production of tablets according to claim 6.

Claims for the following Contracting State : ES

1. A process for the preparation of sustained release granules comprising ibuprofen and a pharmaceutically acceptable polymeric material operable to provide a slow release of the ibuprofen over the pH range 1.0 to 7.5, the polymeric material being present in an amount of 5% to 25% by weight, based on the ibuprofen, which comprises dissolving the ibuprofen and the polymeric material in a solvent and evaporating the solvent to form granules of coprecipitated ibuprofen and polymeric material.
2. A process according to claim 1 in which the polymeric material is present in an amount of 5% to 15% by weight, based on the weight of the ibuprofen.
3. A process according to claims 1 or 2, in which the polymeric material comprises ethyl cellulose, a copolymer of dimethylaminoethyl methacrylate and methacrylic acid ester or high viscosity hydroxy propyl methyl cellulose.
4. A process according to claim 3 in which the polymeric material comprises ethyl cellulose.
5. A process for the production of tablets comprising compression of granules prepared according to claim 1.
6. A process for the production of tablets which comprises the compression of granules prepared according to claim 2.
7. A process for the production of tablets comprising the compression of granules prepared according to claim 3.

8. A process for the production of tablets which comprises the compression of granules prepared according to claims 1 to 3 together with a disintegrating agent.

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IMPRESO POR MANABALLO S.A. NIT. 980.013.711-5 10027 02-2308

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha: 20081016

Hora Certificado: 11:47:54

Operacion: 02CP21016031

PAGINA No. 2

CERTIFICA:

QUE POR ESCRITURA NRO. 3255 DEL 30 DE AUGUST DE 1983 NOTARIA DECIMA DE CALI INSCRITA EN LA CAMARA DE COMERCIO EL 31 DE AUGUST DE 1983 BAJO EL NRO. 62343 DEL LIBRO IX LA SOCIEDAD SE TRANSFORMO EN COMANDITA POR ACCIONES EN SOCIEDAD ANONIMA BAJO EL NOMBRE DE TECNOQUIMICAS S.A.

CERTIFICA:

QUE POR ESCRITURA NRO. 5664 DEL 12 DE DECEMBER DE 2005 NOTARIA TERCERA DE CALI INSCRITA EN LA CAMARA DE COMERCIO EL 19 DE DECEMBER DE 2005 BAJO EL NRO. 14102 DEL LIBRO IX SE APROBO LA FUSION POR ABSORCION ENTRE (ABSORBENTE) TECNOQUIMICAS S.A. DE YMBE (ABSORBIDA (S)) DISTRIBUIDORA FARMACEUTICA CALOX COLOMBIANA S.A. EN LIQUIDACION ORGANIZACION FARMACEUTICA AMERICANA S.A. OFA EN LIQUIDACION

CERTIFICA:

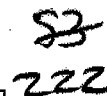
QUE POR ESCRITURA NRO. 1675 DEL 08 DE MAY DE 2008 NOTARIA TERCERA DE CALI INSCRITA EN LA CAMARA DE COMERCIO EL 16 DE MAY DE 2008 BAJO EL NRO. 5362 DEL LIBRO IX LA SOCIEDAD CAMBIO SU NOMBRE DE TECNOQUIMICAS S.A. POR EL DE TECNOQUIMICAS S.A. SIGLA TO S.A.

CERTIFICA:

REFORMAS DOCUMENTO FECHA DOC ORIGEN INS LIBRO

E.P. 4075	05/09/1957	NOTARIA SEGUNDA DE CALI	27/09/1957
16922			
E.P. 5718	28/11/1957	NOTARIA SEGUNDA DE CALI	30/12/1957
17242			
E.P. 5507	31/12/1957	NOTARIA PRIMERA DE CALI	13/03/1958
17529			
E.P. 3124	16/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958
18365			
E.P. 3325	29/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958
18366			
E.P. 5726	17/12/1958	NOTARIA PRIMERA DE CALI	12/05/1959
19258			
E.P. 2374	12/05/1959	NOTARIA PRIMERA DE CALI	03/06/1959
19368			
E.P. 2793	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961

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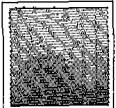
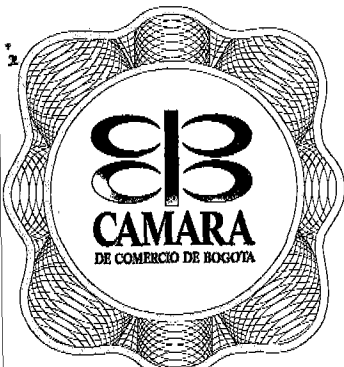


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16998 IX	31/12/1974	NOTARIA SEGUNDA DE CALI	31/01/1975
11772 IX	31/12/1974	NOTARIA SEGUNDA DE CALI	04/04/1975
12441 IX	05/12/1975	NOTARIA SEGUNDA DE CALI	09/01/1976
15581 IX	09/05/1980	NOTARIA SEGUNDA DE CALI	22/10/1980
41529 IX	10/03/1982	NOTARIA DECIMA DE CALI	03/08/1982
54655 IX	10/11/1982	NOTARIA DECIMA DE CALI	30/06/1983
61172 IX	18/03/1986	NOTARIA DECIMA DE CALI	01/04/1986
83730 IX	24/09/1986	NOTARIA DECIMA DE CALI	29/09/1986
87933 IX	04/11/1987	NOTARIA DECIMA DE CALI	19/11/1987
2552 IX	04/11/1987	NOTARIA DECIMA DE CALI	19/11/1987
2553 IX	14/07/1989	NOTARIA DECIMA DE CALI	26/07/1989
20225 IX	29/09/1989	NOTARIA DECIMA DE CALI	02/10/1989
22250 IX	04/12/1992	NOTARIA DECIMA DE CALI	15/12/1992
60929 IX	18/12/1995	NOTARIA DECIMA DE CALI	20/12/1995
10214 IX	22/05/1997	NOTARIA TERCERA DE CALI	27/05/1997
3813 IX	30/06/2000	NOTARIA TERCERA DE CALI	07/07/2000
4740 IX	15/09/2000	NOTARIA TERCERA DE CALI	18/09/2000
6381 IX	30/07/2004	NOTARIA TERCERA DE CALI	04/08/2004
6542 IX	24/05/2006	NOTARIA TERCERA DE CALI	30/05/2006
6565 IX	08/05/2008	NOTARIA TERCERA DE CALI	16/05/2008
5362 IX			
VIGENCIA 01 DE JANUARY DEL AÑO 2057			
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081016

Hora Certificado 11:47:54

Operacion : 02CP21016031

PAGINA No. 5

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD TIENE POR OBJETO: A) LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLOGICOS Y QUIMICOS, MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRICOLAS Y ALIMENTOS NATURALES Y/O PRODUCTOS DE CONSUMO POPULAR DE CUALQUIER NATURALEZA Y SERVICIOS EN GENERAL. B) INVERTIR EN SOCIEDADES O EMPRESAS DE CUALQUIER NATURALEZA O ESPECIE DE LA SOCIEDAD MERCANTIL, NACIONAL O EXTRANJERA, QUE TENGAN COMO ACTIVIDAD O NEGOCIO PROPIO DE SU OBJETO LA FABRICACION, DISTRIBUCION Y 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:

ORGANOS DE DIRECCION Y ADMINISTRACION. PARA LOS FINES DE SU DIRECCION, ADMINISTRACION Y REPRESENTACION, LA SOCIEDAD TIENE LOS SIGUIENTES ORGANOS: A) ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) TRES VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS.

LA DIRECCION 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 REPRESENTACION LEGAL DE LA SOCIEDAD Y LA GESTION DE LOS NEGOCIOS SOCIALES, ESTARAN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081016 Hora certificado 11:47:54

Operacion : 02CP21016031

PAGINA No. 6

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) 2) 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.

LA JUNTA DIRECTIVA SE COMPONE DE SEIS (6) MIEMBROS PRINCIPALES O DIRECTORES, ELEGIDOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS PARA PER?ODOS DE DOS A?OS, SIN PERJUICIO DE QUE PUEDAN SER REMOVIDOS LIBREMENTE POR LA ASAMBLEA O REELEGIDOS INDEFINIDAMENTE. SIMULT?NEAMENTE CON LA ELECCI?N DE LOS PRINCIPALES, LA ASAMBLEA ELEGIR? SEIS (6) SUPLENTES NUM?RICOS, LOS CUALES, EN EL ORDEN DE DESIGNACI?N, REEMPLAZAR?N A LOS PRINCIPALES EN SUS FALTAS ABSOLUTAS, ACCIDENTALES O TEMPORALES.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDR? ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDR? LAS SIGUIENTES FUNCIONES ENTRE OTRAS: C) NOMBRAR Y REMOVER LIBREMENTE AL PRESIDENTE EJECUTIVO, A LOS VICEPRESIDENTES EJECUTIVOS Y A LOS VICEPRESIDENTES ADMINISTRATIVOS. E) DISPONER EL ESTABLECIMIENTO O LA CLAUSURA DE SUCURSALES O AGENCIAS, DENTRO O FUERA DEL DOMICILIO SOCIAL. F) FIJAR LAS POLITICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECON?MICA Y LABORAL; APROBAR PLANES DE INVERSI?N Y DE PRODUCCI?N; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCI?N Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEM?S ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACI?N Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD. G) DETERMINAR LA APLICACI?N QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CAR?CTER DE RESERVAS DE INVERSI?N, HAYAN SIDO APROPIADAS POR LA ASAMBLEA DE ACCIONISTAS. H) AUTORIZAR PREVIAMENTE LAS OPERACIONES QUE TENGAN POR OBJETO: 1) ADQUIRIR, HIPOTECAR Y EN CUALQUIER OTRA FORMA GRAVAR O LIMITAR EL DOMINIO DE BIENES RA?CES CUYA CUANT?A SEA SUPERIOR A \$100.000.000,00 MONEDA CORRIENTE; 2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANT?A SEA SUPERIOR A \$100.000.000,00 MONEDA CORRIENTE; 3) AUTORIZAR INVERSIONES EN BIENES DE CAPITAL O EFECTUAR REPARACIONES O MEJORAS DE LOS MISMOS, CUANDO UNAS U OTRAS IMPLIQUEN, EN CADA CASO, COSTOS O DESEMBOLSOS EN CUANT?A O SUPERIOR A CIENTO MIL D?LARES AMERICANOS (\$US100.000,00) 4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD POR LOS REPRESENTANTES LEGALES CUANDO SU CUANT?A SEA SUPERIOR A \$100.000.000,00 MONEDA LEGAL COLOMBIANA O A US\$300.000,00. L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPA??A A LA CELEBRACI?N DE CONCORDATO PREVENTIVO CON SUS ACREEDORES. M)

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081016

Hora Certificado 11:47:54

Operacion : 02CP21016031

PAGINA No. 7

SERVIR DE ?RGANO CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPA??A.

LA ADMINISTRACI?N INMEDIATA DE LA COMPA??A, SU REPRESENTACI?N LEGAL Y LA GESTI?N DE LOS NEGOCIOS SOCIALES ESTAR?N A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS TRES VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN A?O, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODR?N ACTUAR CONJUNTA O SEPARADAMENTE CON IGUALDAD DE FUNCIONES Y CALIDADES. TODOS LOS EMPLEADOS DE LA COMPA??A CON EXCEPCI?N DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTAR?N SOMETIDOS EN EL DESEMPE?O DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACI?N INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACI?N LEGAL DE LA COMPA??A, LA GESTI?N COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCI?N ADMINISTRATIVA, LA COORDINACI?N Y LA SUPERVISI?N GENERAL DE LA EMPRESA, LAS CUALES CUMPLIR?N CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECI?N A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

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.

PAR?GRAFO: 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:

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BOGOTA

Fecha: 20081018

Hora: 17:54

Operacion: 02CP21016031

PAGINA No. 8

DOCUMENTO: ACTA No. 393 DEL 20 DE JANUARY DE 1993

ORIGEN: JUNTA DIRECTIVA

INSCRIPCION: 26 DE JANUARY 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 BAPTISTA DE LOS RIOS GUTIERREZ

C.C. 17108621

VICEPRESIDENTE EJECUTIVO

EMILIO SARDI APARICIO

C.C. 14434582

DOCUMENTO: ACTA No. 67 DEL 28 DE MARCH DE 2008

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 16 DE MAY DE 2008 No. 5363 DEL LIBRO IX

FUE (RON) NOMBRADO (S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

FRANCISCO JOSE BARBERI OSPINA

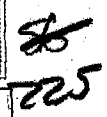
C.C. 14445880

SEGUNDO RENGLON

JUAN MANUEL BARBERI OSPINA

C.C. 14949561

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INTERSCO BOOKS INTERNATIONAL S.A. INT. 890 013 711-5 19027 07-2008

CONFIDENTIAL*



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081016

Hora Certificado 11:47:54

Operacion : 02CP21016031

PAGINA No. 11

CON LA CEDULA DE CIUDADANIA NRO.

14.440.778 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA, EL REPRESENTANTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN LA ADMINISTRACION DE IMPUESTOS Y ADUANAS NACIONALES O DEL ORGANISMO QUE HAGA SUS VECES Y FIRMAR EN REPRESENTACION DE LA SOCIEDAD, LAS DECLARACIONES DEL IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS QUE CORRESPONDA A LA SOCIEDAD, Y TODAS LAS DEMAS DECLARACIONES QUE LA SOCIEDAD DEBA PRESENTAR ANTE DICHA ENTIDAD, TALES COMO LA DE VENTAS, RETENCION EN LA FUENTE, TIMBRE Y CUALESQUIER OTRA DECLARACION QUE POR LEY LA SOCIEDAD ESTE OBLIGADA A PRESENTAR.

B) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A., COMO DECLARANTE DEL IMPUESTO DE INDUSTRIA Y COMERCIO Y EL COMPLEMENTARIO DE AVISOS Y TABLEROS EN LOS MUNICIPIOS EN QUE LA SOCIEDAD ESTE OBLIGADA AL PAGO DE LOS CITADOS IMPUESTOS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE LOS MENCIONADOS TRIBUTOS. C) PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A TECNOQUIMICAS S.A. COMO DECLARANTE DEL IMPUESTO PREDIAL Y COMPLEMENTARIOS EN LOS MUNICIPIOS DONDE TENGA BIENES INMUEBLES, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DEL CITADO IMPUESTO. D) PARA DAR RESPUESTA A LOS REQUERIMIENTOS ORDINARIOS Y A LAS SOLICITUDES DE INFORMACION EN RELACION CON LOS IMPUESTOS ADMINISTRADOS POR LA DIRECCION DE IMPUESTOS Y ADUANAS NACIONALES Y POR LAS DEPENDENCIAS MUNICIPALES QUE ADMINISTREN LOS IMPUESTOS DE CARACTER TERRITORIAL. E) Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO LA SOCIEDAD QUEDE SIN REPRESENTACION EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS.

CERTIFICA:

QUE POR ESCRITURA NRO. 307 DEL 31 DE JANUARY DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRUARY DE 2002 BAJO EL NRO. 298 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A JORGE ROBERTO OBANDO RODRIGUEZ, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NRO. 14.960.183 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACION DE LA SOCIEDAD, CUYA PERSONERIA OSTENTA: 1o.) PROMUEVA O DESISTA DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL O GUBERNATIVO, YA SEA EN PROCESOS, ACTUACIONES O ACTOS SIMPLES, DILIGENCIAS O GESTIONES EN QUE TECNOQUIMICAS S.A. TENGA INTERES COMO ACTOR, DEMANDANDO O TERCERO INTERVINIENTE EN RELACION CON LOS ASUNTOS DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE DE ELLOS EN NOMBRE DE TECNOQUIMICAS S.A. 2o.) SUSCRIBA Y DE POR TERMINADO LOS CONTRATOS DE TRABAJO DEL PERSONAL VINCULADO A LA EMPRESA. 3o.) CONSTITUYA APODERADOS EN DESARROLLO DE ESTA REPRESENTACION LABORAL, REVOQUE Y SUSTITUYA DICHOS PODERES CUANDO LO ESTIME PROCEDENTE. 4o.) TRANSIGA, CONCILIE, DESISTA Y COMPROMETA A LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARACTER LABORAL, POLICIVO, PENAL O DE FISCALIA EN LOS QUE LA EMPRESA SEA

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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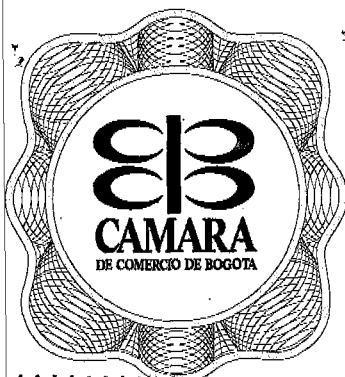
PAGINA No. 12

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.) OTORQUE 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. REPRESENTA 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 NOMERADA 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.) REPRESENTA 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 4.202 DEL 31 DE MAY DE 1995, NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTEMBER 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 REPRESENTA A TECNOQUIMICAS S.A. EN LOS SIGUIENTES ACTOS: A)

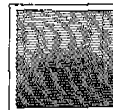
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081016

Hora Certificado 11:47:54

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PAGINA No. 13

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 PRESENTE PODER SI LO ESTIMARE CONVENIENTE Y EN CASO NECESARIO REVOCAR DICHAS SUSTITUCIONES. PUDIENDO ATENDER ASI MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENERE DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACION DE CAUSALIDAD POR LOS SUSODICHOS TRAMITES Y 3) EN GENERAL PARA QUE ASUMA LA PERSONERIA EN NOMBRE DE TECNOQUIMICAS S.A., SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. ANTONIO JAIRO RAMIREZ ECHAVE SE CENIRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O SU REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 6224 DEL 15 DE DECEMBER DE 2004 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 17 DE JANUARY DE 2005 BAJO EL NRO. 3 DEL LIBRO V MEDIANTE LA CUAL CONCEDE PODER ESPECIAL PERO AMPLIO Y SUFICIENTE A DIEGO PEREZ MENDOZA MAYOR DE EDAD, VECINO DE BOGOTA, IDENTIFICADO CON CEDULA DE CIUDADANIA NUMERO 16.820.530 DE CALI, COMO SU REPRESENTANTE CON PODER ESPECIAL, AMPLIO Y SUFICIENTE, PARA REALIZAR TODOS LOS TRAMITES RELACIONADOS CON EL PROCEDIMIENTO DE OTORGAMIENTO DE LICENCIA DE VENTA DE LOS PRODUCTOS AGRICOLAS DE LA SOCIEDAD, CON FACULTAD PARA FIRMAR TODO TIPO DE DOCUMENTOS, SOLICITUDES, REQUERIMIENTOS, MEMORIALES RESPUESTAS, ACLARACIONES BIEN SEA ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO ICA, MINISTERIO DEL MEDIO AMBIENTE, MINISTERIO DE PROTECCION SOCIAL O ANTE LAS AUTORIDADES GUBERNAMENTALES COMPETENTES EN LO RELACIONADO CON LOS TRAMITES QUE PERMITAN LA COMERCIALIZACION DE ESE TIPO DE PRODUCTOS. LA FACULTAD TAMBIEN COMPRENDERA LA DE NOTIFICARSE, RESPONDER E INTERPONER RECURSOS DE TODO TIPO DE ACTO ADMINISTRATIVO. EL APODERADO SUSCRIBIRA TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES MENCIONADAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS

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CERTIFICADO NACIONAL

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PAGINA No. 20

PAR?GRAFO I. EN LA ATENCI?N DE TODOS LOS ASUNTOS MENCIONADOS TENDR? LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CAR?CTER JUDICIAL O GUBERNATIVO.

PAR?GRAFO II. LOS APODERADOS EJERCER?N SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACI?N.

4. ADRIANA JIM?NEZ MERA, IDENTIFICADA CON LA C.C. 31.174.077 DE PALMIRA, PARA EL DESARROLLO DE LAS SIGUIENTES FUNCIONES:

A. OTORGAR PODER Y CONSTITUIR MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES COMERCIALES Y PENALES TENDIENTES A LA RECUPERACI?N DE LA CARTERA, SIN LIMITACION DE CUANT?A, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACI?N, CON AUTORIZACI?N 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 LAS DEUDAS A FAVOR DE TECNOQU?MICAS S. A.

B. SUSCRIBIR LOS CONTRATOS DE ARRENDAMIENTO DE INMUEBLES, SU MODIFICACI?N Y O TERMINACI?N, INVENTARIOS Y ANEXOS PERTINENTES, BIEN SEA QUE LA SOCIEDAD OBRE COMO ARRENDADOR O ARRENDATARIO, SIN LIMITACI?N DE CUANT?A. ESTA FUNCI?N LA PODR? EJERCER DIRECTAMENTE O MEDIANTE LA DESIGNACI?N DE APODERADOS.

C. SUSCRIBIR LOS FORMATOS DE AUTORIZACI?N DE CREACI?N DE CLIENTES Y PROVEEDORES DE LA EMPRESA.

D. EN RELACI?N CON LOS VEH?CULOS DE TODO TIPO QUE FIGUREN A NOMBRE DE TECNOQU?MICAS, TIENE LA FACULTAD DE SUSCRIBIR LOS FORMULARIOS OFICIALES PARA TODO TIPO DE TRAMITE, ENTRE ELLOS EL TRASPASO, QUE SE REQUIERA REALIZAR, ANTE LAS SECRETARIAS DE TRANSITO Y ANTE LAS AUTORIDADES DE TRANSITO Y TRANSPORTE DE CUALQUIER ORDEN, AS? COMO FIRMAR TODO TIPO DE CONTRATOS RELACIONADOS CON LOS VEH?CULOS.

PAR?GRAFO. EN LA ATENCI?N DE TODOS LOS ASUNTOS MENCIONADOS TENDR? LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CAR?CTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

ESTOS PODERES ESTAR?N VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS EXPRESAMENTE POR DOCUMENTO PRIVADO.

QUE POR DOCUMENTO PRIVADO DEL 10 DE JULY DE 2008 DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 29 DE JULY DE 2008 BAJO EL NRO. 141 DEL LIBRO V, SE

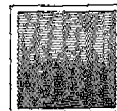
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081016

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Operacion : 02CP21016031

PAGINA No. 21

CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A LOS SIGUIENTES FUNCIONARIOS DE LA EMPRESA:

- GERMAN ALBERTO SUAREZ HINCAPIE, C.C. 16.722.521 DE CALI, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL CENTRO PACIFICO DE LA SOCIEDAD, CON SEDE EN CALI.
- MARIA VICTORIA VARGAS PORRAS, C.C. 39.638.185 DE BOGOTA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.
- ESPERANZA GRANADOS JAIMES, C.C. 63.392.189 DE MALAGA (SANTANDER), SUBGERENTE ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.
- DIEGO FERNANDO MUÑOZ QUINTERO, C.C. 94.282.452 DE CALI, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDELLIN.
- CARLOS ORLANDO MUTIS PICON, C.C. 91.200.418 DE BUCARAMANGA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA.
- DANIEL AMEZQUITA LIZARAZO, C.C. 8.681.962 DE BARRANQUILLA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ATLANTICO DE LA SOCIEDAD, CON SEDE EN BARRANQUILLA.

LOS MENCIONADOS FUNCIONARIOS EJERCERAN, EN SUS RESPECTIVAS REGIONALES, LAS SIGUIENTES FACULTADES:

1. PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A., Y EN ASUNTOS QUE TENGA QUE VER CON SUS RESPECTIVOS DISTRITOS DE VENTAS SE NOTIFIQUEN Y PROMUEVAN ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES, DISTRITALES 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 OTORGUEN PODERES Y CONSTITUYAN 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 E INTERROGATORIOS DE PARTE, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA

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CERTIFICADO NACIONAL

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PAGINA No. 26

FECHA MATRICULA 22 DE ABRIL DE 1992

RENOVO POR EL AÑO 2008

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 41 66 DE CALI

FECHA MATRICULA 22 DE ABRIL DE 1992

RENOVO POR EL AÑO 2008

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO

EL NRO. 606730-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A JAMUNDI

UBICADO EN: CARRETERA JAMUNDI KM. 23 DE JAMUNDI

FECHA MATRICULA 04 DE ABRIL DE 2008

RENOVO POR EL AÑO 2008

CERTIFICA

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO

EL NRO. 606736-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS S A YUMBO

UBICADO EN: CL. 15 NRO. 30-98 AUTOPISTA CALI-YUMBO KILOMETRO 4 DE YUMBO

FECHA MATRICULA 14 DE ABRIL DE 2003

RENOVO POR EL AÑO 2008

CERTIFICA

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 29 DE

MARCH DE 2008

CERTIFICA

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL

PRESENTE CERTIFICADO

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES

DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO

TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA

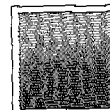
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20081016

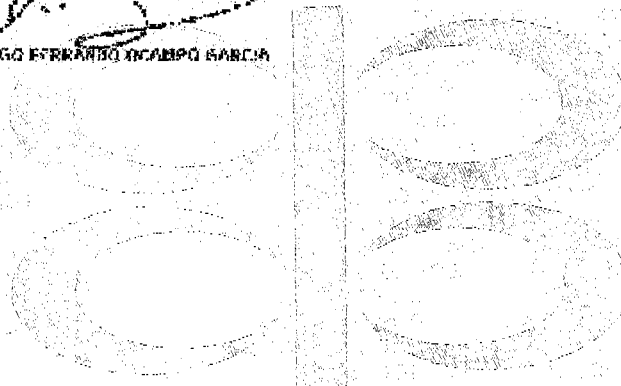
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Operacion : 02CP21016031

PAGINA No. 27

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.
DADO EN CALI A LOS 16 DIAS DEL MES DE OCTOBER DEL AÑO 2008 HORA: 11:49:10


DIEGO FERNANDO CAMPO GARCIA



IMPRESO POR: EMERSON S.A. INT. 88010111-3 (08717628)

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

236

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-032749- -00007-0000

Fecha: 2008-10-28 16:22:22 Dep: 2020 NÚMERO DE RELACIONE
11a 11 PATENTILLAS L78 378 FASE NACIONAL
A: 1 400 OPOSICION SERVILIR Folios: 67

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 85,315
FECHA : OCTUBRE 28 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	91207314	28/10/2008	682,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	91207325	28/10/2008	1,023,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	75,000.00
TOTAL :			\$ 75,000.00

SON: SETENTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____