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**FORMULARIO UNICO DE OPOSICION
2000-12**

1	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	
2	SOLICITUD PUBLICADA
Número del expediente: 06-064-910 Solicitante: ZAMBON GROUP S. P. A. Apoderado: DILIA MARÍA RODRÍGUEZ D'ALEMÁN Título de la nueva creación o denominación del signo: PREPARACIÓN FARMACÉUTICA QUE CONTIENE GABAPENTIN. Gaceta 592 de 30 de Mayo de 2008, número de publicación 428.	
3	OPOSICION PRESENTADA POR:
OPOSITOR	IDENTIFICACION
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	C.C. ☐ NIT ☒ C.E. ☐ Otro ☐ Número: 890 300 466-5
REPRESENTANTE O APODERADO (74)	IDENTIFICACION
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.	C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Número: 79'152.473 de Usaquén TP 44655
4	FUNDAMENTOS DE LA OPOSICION:
Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial) 16, 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.

OP-68.492
68-68.495

(Oposición) Fecha

Agosto 28 de 2008

(Prórroga) Fecha

Agosto 22 de 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

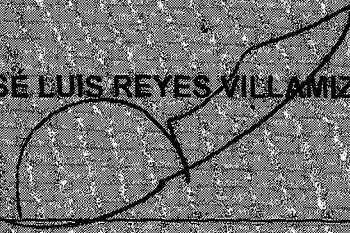


Copia de la oposición para el traslado al solicitante.

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA:



Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 06-064-910

TÍTULO SOLICITADO: PREPARACIÓN FARMACÉUTICA QUE CONTIENE GABAPENTIN.

PUBLICACIÓN: Gaceta 592 de 30 de Mayo de 2008, número de publicación 428.

PRIORIDAD: IT MI 2003A002399 de 09/12/2003

SOLICITANTE: ZAMBON GROUP S. P. A.

APODERADO: DILIA MARÍA RODRÍGUEZ D'ALEMÁN

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 **06-064-910**, por no cumplir con lo dispuesto por los artículos 14 y 18 de la Decisión 486 de 2000, con base en los fundamentos que se expondrán a continuación.

II. LEGÍTIMO INTERÉS

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

III. FUNDAMENTO DE LA OPOSICIÓN

La solicitud colombiana en trámite que reivindica un granulado de gabapentina obtenido mediante la granulación de gabapentina con polietileno glicol, que tiene un punto de fusión comprendido entre 50° C y 80° C; incumple con los requisitos indispensables para otorgársele el privilegio de patente de invención tal y como se demuestra con los siguientes argumentos:

- 3.1** Para comenzar, el proceso de granulación que describe la solicitud colombiana en trámite es ampliamente conocido en el estado de la técnica como "granulación por fusión" (melt granulation) y es un proceso también ampliamente usado cuyo objetivo es transformar una mezcla de polvos en una masa o en conjunto compacto y homogéneo a través de la aplicación de calor y agitación a la mezcla de polvos, los cuales, o al menos uno de ellos, tiene un punto de fusión bajo que permite formar una mezcla o dispersión fluida (fundida) que permite la unión de las partículas de la mezcla en gránulos que posteriormente se dejan enfriar, por lo menos, a temperatura ambiente.

Los mecanismos de la aglomeración de las partículas por este método de granulación son similares a los de la granulación por vía húmeda, de hecho, el (los) material(es) sólido(s) dentro de la mezcla de polvos que tiene(n) la capacidad de fundirse a bajas temperaturas, cuando se aplica la temperatura adecuada, actúa como un agente o solución aglutinante clásica. Los equipos predilectos para este tipo de granulación son los

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99

también reconocidos mezcladores de alto corte (High-shear Mixers) equipados con chaquetas calefactoras que permiten modificar y controlar la temperatura del proceso. Prueba del vasto conocimiento de esta técnica, es expuesta en documentos (patentes) que describen, desde la década de 1960 tanto el proceso como los equipos a través de los cuales se puede llevar cabo la formulación de granulados¹.

En el mismo sentido, existen publicaciones de carácter científico que demuestran que las condiciones y variables bajo las cuales se realizan dichos procesos de granulación, han sido ampliamente descritas y estudiadas en el estado de la técnica, veamos:

Advantages In Energy, Fuel, And Investment Savings By Melt-Type Granulation Processes².

Abstract: Melt-type processes developed by TVA, in which wet-process phosphoric acid provides all or most of the P_2O_5 in granular fertilizers, show promise in decreasing fuel, total energy, investment, and operating cost. The analyses and estimates were based on pilot-plant studies and demonstration-plant experience at TVA's National Fertilizer Development Center, Muscle Shoals, Alabama. It is shown that elimination of fuel for drying and substantially decreased horsepower requirements (particularly in a new plant) would decrease energy requirement in the granulation plant by about 1,000,000 Btu's per metric ton of P_2O_5 . When coupled with lower operating costs that are based on investment factors, the savings for the granulation plant is indicated to be about \$6 per metric ton of P_2O_5 for a melt-type ammonium phosphate plant. As explained in the text, there would be just about a tradeoff in energy required for drying in a conventional ammonium phosphate granulation plant (where wet-process acid also is produced) against the equivalent steam that would be needed to concentrate the feed acid from 40% P_2O_5 to 52 to 54% P_2O_5 for use in melt-type granulation. This would decrease the overall estimated savings for a melt-type ammonium phosphate granulation plant to about \$3.65 per metric ton P_2O_5 . In the case of NPK granulation plants using 52 to 54% P_2O_5 acid shipped in, the full indicated savings of about \$5.10 per metric ton nutrient should be realized. Savings in existing and new plants are indicated.

Alternative Granulation Technique: Melt Granulation³.

Abstract: A melt granulation process has been investigated which efficiently agglomerates pharmaceutical powders for use in both immediate- and sustained-release solid dosage forms. The process utilizes materials that are effective as

¹ Patente americana US 3,263,006 publicada el 26 de Julio de 1966; Patente americana US 3,405,208 publicada el 08 de octubre de 1968; Patente americana US 3,601,847 publicada el 27 de octubre de 1969 y la Patente americana US 3,700,364 publicada el 24 de octubre de 1972.

² Young, R.D. ; Lee, R.G. Technical conference of International Superphosphate and Compound Manufacturers Association Limited and the Fertilizer Association of India; 8 Dec 1975; New Delhi, India (Conference). Publication Date 1975 Jan 01.

³ Alan Royce; Jiwaji Suryawanshi; Udayan Shah; Krishna Vishnupad; Drug Development and Industrial Pharmacy, Volume 22, Issue 9 & 10 September 1996, pages 917 - 924.

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160

granulating fluids when they are in the molten state. Cooling of the agglomerated powders and the resultant solidification of the molten materials completes the granulation process. Both the molten agglomeration and cooling solidification were accomplished in a high shear Collette Grai mixer equipped with a jacketed bowl. Hence, the melt granulation process replaces the conventional granulation and drying operations which use water or alcohol solutions. The melt granulation process has been investigated using immediate- and sustained-release TAVIST® (clemastine fumarate USP) tablet formulations. The TAVIST granulations have been characterized by power consumption monitoring, measurement of the granulation particle size distribution, bulk and tapped density determinations, and loss-on-drying measurements. Scale-up of the melt granulation process for the sustained release TAVIST tablet formulation was judged successful based on a comparison of the hardness, friability, weight uniformity during compression, disintegration time, and dissolution rate data obtained at different manufacturing scales.

Melt Granulation In A Laboratory Scale High Shear Mixer⁴.

Abstract: The applicability of a 10 litre high shear mixer for melt granulation of dicalcium phosphate and lactose is examined. Polyethylene glycol (PEG) 3000 and 6000 were used as melting binders in concentrations of 15-20% w/w. The effects of binder concentration, massing time, impeller speed, and particle size of the PEG 6000 on granule size, granule size distribution and intragranular porosity are investigated.

It is shown that pellets of a narrow size distribution can be produced by the use of a high impeller speed. Granule size and size distribution are markedly influenced by binder concentration and massing time. The particle size of the PEG has only a minor effect on the granule growth. Granule growth mechanisms by melt granulation are discussed on the basis of the liquid saturations and the amounts of binder liquid and are compared with previous results on wet granulation.

Preparation And Characterisation Of Ibuprofen-Poloxamer 188 Granules Obtained By Melt Granulation⁵.

Abstract: The aim of this study was to prepare, by melt granulation, granules containing ibuprofen as a poorly water soluble model drug in order to improve its dissolution rate and its availability; lactose as a diluent and poloxamer 188 (Lutrol F68), as a new meltable hydrophilic binder, were used. The granules were prepared in a laboratory-scale high-shear mixer, using a jacket temperature of 50 degrees C and an impeller speed of 500 rpm. The particle size analysis shows that the main fraction was between 200 and 500 microm, while the determination of drug content indicated that ibuprofen was quite uniformly distributed in all the fractions. Scanning Electron Microscopy (SEM), image and fractal analysis revealed that the granules did not have a perfect spherical shape and a rugged surface ($D(s)=2.6475$). The in vitro dissolution tests showed an increase in the dissolution rate of granules compared to pure drug and physical mixture. The characterisation of the samples, performed by Differential Scanning Calorimetry (DSC) and X-ray powder diffraction (XRD), suggests that the improvement of dissolution rate could be correlated to the formation of a eutectic mixture between the drug and the binder. Stability studies indicated that the granule properties do not change, at least after 1 year of storage at 25 degrees C. In conclusion, the

⁴ T. Schaefer, P. Holm, H. G. Kristensen. Drug Development and Industrial Pharmacy, Volume 16, Issue 8 May 1990, pages 1249 - 1277.

⁵ Passerini N, Albertini B, González-Rodríguez ML, Cavallari C, Rodríguez L. Eur J Pharm Sci. 2002 Feb;15(1):71-8.

5 7 15
157

results of this work suggest that the melt granulation technique is an easy and fast method to improve the dissolution rate of ibuprofen, using poloxamer 188 as a new hydrophilic melttable binder.

The Control Of Drug Release From Conventional Melt Granulation Matrices⁶.

Abstract: Sustained release potassium chloride tablets were prepared using a melt granulation formulation in a Baker Perkins Granulator. Parts of the validation for this manufacturing process are highlighted in this paper including granulation end point temperature, incorporation of extragranular excipients, amount of wax in the formulation, granule cooling rate and scale of the operation. A number of other factors have been studied which are not included here although they are no less important. The release of potassium chloride from tablets was found to be dependent on the wax level and the amount of extragranular excipients ("wicking agent"). Within the controlled production process, any variation in granulation end point temperature and granule cooling rate should not have any significant effect.

Effect Of Crystallization Behavior Of Polyethylene Glycol 6000 On The Properties Of Granules Prepared By Fluidized Hot-Melt Granulation (FHMg)⁷.

Abstract: The objective of this study was to investigate the effect of the crystallization behavior of Macrogol 6000 (polyethylene glycol 6000; PEG 6000), used as a binder, during the solidification process on the properties of mononucleic granules prepared by the fluidized hot-melt granulation (FHMg) technique. Crystallization of PEG 6000 from molten liquid was investigated using differential scanning calorimetry (DSC) and hot stage microscopy. The results obtained from the measurement of isothermal crystallization demonstrated that crystallization of PEG 6000 was either slow or rapid. Analysis based on solid-state decomposition showed that slow crystallization was due to the two-dimensional growth of nuclei mechanism, while rapid crystallization was due to the three-dimensional growth of nuclei mechanism. Observation of the crystallization of PEG 6000 by hot stage microscopy supported the existence of two different crystallization mechanisms. Granules containing PEG 6000 that underwent rapid crystallization during FHMg showed a significantly higher fraction powder under 150µm in diameter. This was caused by the loss of powder particles from the surface of mononucleic granules during the solidification process, because many cracks were observed after crystallization of PEG 6000 with a short isothermal crystallization time (ICT) due to the reduced of sticking of particles. The results of this study suggested that the crystallization behavior of the binder during the solidification process of FHMg can influence the properties of the resultant granules, such as particle size distribution, content uniformity or taste masking. It was also indicated that measuring the ICT using DSC was a useful method to classify PEG 6000.

Como se puede observar, en estas publicaciones se revela tanto las características fundamentales de esta técnica como la utilidad de la misma

⁶ P. Flanders; G. A. Dyer; D. Jordan. Drug Development and Industrial Pharmacy, Volume 13, Issue 6 May 1987, pages 1001 - 1022.

⁷ Motonori KIDOKORO, Kaoru SASAKI, Yasuo HARAHISHI, and Norio MATAHIRA. Chem. Pharm. Bull. 51(5) 487-493 May 2003.

6 8 102
102

en la elaboración de diversas formulaciones farmacéuticas con principios activos que presentan inconvenientes para la granulación por vía húmeda.

Además, es importante resaltar que en dos de las publicaciones se hace mención explícita del uso de polietilenglicoles, que es precisamente la clase de polímeros que reivindica la solicitud colombiana en trámite para la elaboración de sus respectivas formas farmacéuticas a través de esta técnica. Si bien es cierto que no se hace mención explícita de el uso de pregabalina como principio activo, para cualquier persona medianamente versada en la materia queda claro que para aplicar esta técnica de granulación con cualquier otro principio activo, basta con someter los componentes de la formulación a los respectivos ensayos de formulación y preformulación que aseguren que dichos componentes bajo las condiciones del proceso, consigan las características finales de seguridad, estabilidad, eficacia y eficiencia que debe tener todo medicamento de este tipo.

En otras palabras, al estar descrito detalladamente éste método de granulación en el estado del arte, y siendo este mismo método el argumento que sustenta todas las reivindicaciones de la solicitud colombiana en trámite, ésta carece irrefutablemente de nivel inventivo.

Como complemento, es importante resaltar que según el "Handbook of Pharmaceutical Excipients"⁸:

"Polyethylene glycols are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations" (...)

"In solid-dosage formulations, higher molecular weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules".(...)

"When used for thermoplastic granulations, a mixture of the powdered constituents with 10-15% w/w PEG 6000 is heated to 70-75°C. The mass becomes paste-like and forms granules if stirred while cooling. This technique is useful the preparation of dosage forms such as lozenges when prolonged disintegration is required".(...)

"Polyethylene glycols are chemically stable in air and in solution although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, nor do they become rancid.(...)

⁸ Arthur H. Kibbe. "Handbook of Pharmaceutical Excipients". Third Edition 2000. Pag 392, 393.

7 9 103
103

Este texto nos muestra sin más, que los Polietilenglicoles son ampliamente usados en distintos tipos de formulación entre ellos en formulaciones sólidas y en la formación de granulados y que son sustancias estables químicamente, lo que significa que son sustancias viables y ampliamente usadas en la industria farmacéutica como excipientes adecuados de granulación, en consecuencia, su empleo y su inclusión en las formulaciones -independientemente del activo- o como las reivindicadas en la solicitud colombiana en trámite carecería de nivel inventivo.

3.2 La publicación internacional WO 03/035040 publicada el 1 de mayo de 2003 y titulada "METHODS OF TREATMENT USING A GASTRIC RETAINED GABAPENTIN DOSAGE", revela un método de tratamiento de la epilepsia que comprende administrar una cantidad terapéuticamente efectiva de gabapentina o una sal de la misma, en una forma de dosificación de retención gástrica.

Más adelante en el ejemplo 3 (pág 14 y 15) señala:

Example 3

Three Gastric Retentive (GRTM)

Gabapentin Formulas were manufactured utilizing a standard granulation technique.

The formulations manufactured are shown in tabulated form below:

Formulation for Clinical Trial Manufacture		
Gabapentin GR8, 300-mg (GR8, 300-mg)	Gabapentin GR6, 300-mg (GR6, 300-mg)	Gabapentin GR5, 600-mg (GR8, 600-mg)
44.76% Gabapentin	44.76% Gabapentin	61.11% Gabapentin
21.99% Methocel [®] K15M, premium	16.46% Methocel [®] K4M, premium	7.59% Methocel [®] K15M, premium
21.99% Sentry [®] PolyOx [™] WSR Coagulant, NF FP	21.99% Sentry [®] PolyOx [™] WSR 303, NF FP	27.09% Sentry [®] PolyOx [™] WSR 303, NF FP
7.40% Avicel [®] PH-101, NF	12.98% Avicel [®] PH-101, NF	0.00% Avicel [®] PH-101, NF

2.75% Methocel [®] E5, prem.	2.75% Methocel [®] E5, prem.	3.22% Methocel [®] E5, prem.
1.00% Magnesium Stearate, NF	1.00% Magnesium Stearate, NF	1.00% Magnesium Stearate, NF
670-mg (Tablet weight)	670-mg (Tablet weight)	982-mg (Tablet weight)
0.3937" X 0.6299"	0.3937" X 0.6299"	0.4062" X 0.75"
Mod Oval	Mod Oval	Mod Cap

Gabapentin was obtained from Plantex U.S.A. (Englewood Cliffs, NJ). Methocel[®] brand hydroxypropyl methylcellulose (also known as hypromellose), and Sentry[®] PolyOx[®] brand polyethylene oxide were obtained from Dow Chemical (Midland, Michigan). Methocel E5, premium is a USP type 2910 hydroxypropyl methylcellulose with number average molecular weight of on the order of 6000-8000 and a viscosity of 5 cps as a 2% aqueous solution at 20 °C. Methocel[®] K4M and Methocel[®] K15M are USP type 2208 hydroxypropyl methylcellulose with viscosities of 4000 cps and 15,000 cps, respectively, as a 2% aqueous solution at 20 °C, and number average molecular weights on the order of 80,000 and 100,000, respectively. Sentry[®] PolyOx[®] WSR 301, NF FP, Sentry[®] PolyOx[®] WSR Coagulant, NF FP and Sentry[®] PolyOx[®] WSR 303, NF FP have viscosity-average molecular weights of approximately 4,000,000, 5,000,000 and 7,000,000, respectively.

Como vemos, este documento revela tabletas que comprenden Gabapentina hechas mediante el uso de una técnica convencional de granulación en donde la formulación comprende gabapentina en una cantidad superior al 61% w/w, PEG o PolyOx[®] y otros agentes o aditivos necesarios para la preparación de dichas tabletas. Si bien es cierto que en este ejemplo no se especifica si la granulación se hace o no con el PEG, no lo es menos que, los elementos principales revelados en la solicitud colombiana en trámite (Gabapentina, PEG, Granulación, Otros agentes), son o fueron revelados en la anterioridad mencionada, lo que evidentemente desvirtúa al menos el nivel inventivo de la misma.

- 3.3 La publicación internacional WO 2003/068186 publicada el 21 de Agosto de 2003 y titulada "PHARMACEUTICAL FORMULATIONS AND SYSTEMS FOR IMPROVED ABSORPTION AND MULTISTAGE RELEASE OF ACTIVE AGENTS" revela:

9 2405 125

The present invention relates generally to the field of drug delivery. More specifically, the invention relates to novel pharmaceutical compositions for administration of active agents to patients, wherein the compositions provide for multi-stage drug release. The invention additionally relates to processes for preparing the suspensions and methods of using the suspensions to administer an active agent to a patient. The invention has utility in the fields of pharmaceutical formulation, pharmacology, and medicine.

(...)

anxiolytics, sedatives, and hypnotics, such as alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, chlorprothixene, clonazepam, clobazam, clotiazepam, clozapine, dexamethylphenidate (d-threo-methylphenidate) diazepam, droperidol, ethinamate, flunarisone, flunitrazepam, triflupromazine, flupenthixol decanoate, fluphenazine, flurazepam, gabapentin, gaboxadol, γ -hydroxybutyrate, haloperidol, lamotrigine, lorazepam, lormetazepam, medazepam, meprobamate, mesoridazine, methaqualone, methylphenidate, midazolam, modafinil, molindone, nitrazepam, olanzapine, oxazepam, pentobarbitone, perphenazine pimozone, pregabalin, prochlorperazine,

(...)

The active agent particles can be manufactured using any of a wide variety of suitable techniques, including dry and wet granulation, pelletization, application of one or more coatings on an inert or active core, and the like. Commonly utilized coating and pelletization processes include balling, spheronization, extrusion, fusion, precipitation, coprecipitation, spray congealing, spray drying, pan coating, fluidized bed coating, melt extrusion, crystallization, cryopelletization, nanocapsulation, coacervation, etc. Conventional, pharmaceutically acceptable additives can be introduced prior to or during particle manufacture to facilitate particle preparation, depending on the process, the active agent, and the nature of the final particulate material.

(...)

Melt Extrusion: The active agent particles can also be melted and extruded with a continuous, solvent-free extrusion process, with or without inclusion of additives.

(...)

156

The processes described above are suitable for producing substrate-based particles or non-substrate-based particles. In the latter case, the particulate material does not include any seed particle (e.g., a conventional drug or other additive aggregate starch or sugar bead). Instead, the compositions are processed, and the components are chosen, such that a solid composition is formed without need for a substrate bead. The particles formed can be in the form of beadlets, beads, granules, pellets, etc., that have an approximately homogenous distribution. These particulates can be produced by means of balling in pelletizers or fluid bed granulators, and compaction or extrusion.

(...)

Thus, compositions of the present invention can be formulated as, for example, pills, capsules, caplets, tablets, granules, beads, pellets, or powders. Granules, beads, and powders can, of course, be further processed to form pills, capsules, caplets, or tablets.

(...)

In a preferred embodiment, the oral dosage form is comprised of an encapsulated composition, wherein the pharmaceutical formulation is typically contained in a capsule.

(...)

1. A pharmaceutical formulation, comprising:

- (a) an active agent having a first fraction and a second fraction, wherein the first fraction is comprised of a plurality of solid particles; and
- (b) a pharmaceutically acceptable vehicle comprising at least one compound selected from the group consisting of a hydrophilic surfactant, a lipophilic surfactant, a triglyceride and a solubilizer,

(...)

8. The pharmaceutical formulation of claim 1, wherein the solid particles are comprised of powder, granules, pellets, beads, or combinations thereof.

(...)

11. The pharmaceutical formulation of claim 1, wherein the solid particles are prepared by a process selected from melt extrusion, nanoencapsulation, lyophilization, spheronization, coacervation, cryopelletization, crystallization, antisolvent precipitation, precipitation from expanded supercritical fluid, spray drying, spray coating, spray congealing, and combinations thereof.

(...)

33. The pharmaceutical formulation of claim 32, wherein the synthetic hydrophilic polymers are selected from the group consisting of polyethylene glycol, mono-poly(oxyethylene)-substituted propylene glycol, di-(polyoxyethylene)-substituted propylene glycol, mono-poly(oxyethylene)-substituted glycerol, di-(polyoxyethylene)-substituted glycerol, tri-(polyoxyethylene)-substituted glycerol, polyoxyethylated sorbitol, polyoxyethylated glucose, polyvinyl pyrrolidone, poly(N-vinyl caprolactam), and polymers and copolymers of acrylic acid, methacrylic acid and/or esters thereof.

(...)

38. The pharmaceutical formulation of claim 1, wherein the vehicle is substantially free of added water.

Como se puede apreciar, en esta anterioridad si bien es cierto se refiere a composiciones en forma de suspensión es importante resaltar que se revela el uso de la técnica de granulado por fusión para la obtención de gránulos que posteriormente pueden convertirse en tabletas o cápsulas, además, se hace mención explícita del uso de polietilenglicol durante este proceso de obtención y se menciona la inclusión de gabapentina como principio activo de dichas formulaciones; con lo cual el nivel inventivo de la Rv 1 y otras (Rvs 5 a 18) de la solicitud colombiana en trámite quedan desvirtuados.

3.4 La publicación internacional WO 2003/002151 publicada el 09 de Enero de 2003 y titulada "ORAL PHARMACEUTICAL COMPOSITIONS WITH MODIFIED RELEASE OF THE ACTIVE INGREDIENT" revela:

1. Oral controlled-release pharmaceutical compositions, comprising:
 - a) a matrix consisting of amphiphilic compounds either liquid or with melting point below 60°C, possibly to form eutectic mixture melting at 35-37°C, in which the active ingredient is at least partially soluble and/or dispersed and/or inglobated or granulated

(...)

2. Compositions as claimed in claim 1 wherein the amphiphilic compounds comprise glycol alkyl ethers such as diethylene glycols monoethyl ether; macroglycerids such as mixtures of mono- and triglycerids and of mono- and diesters of polyethylene glycols and of fatty acids, polyethylene glycols hydroxystearates.

(...)

6. Composition as claimed in the above claims, wherein the active ingredient is in part present in the amphiphilic matrix and in part loaded on the cyclodextrins and/or polymers, in the form of minitabets, granules or microgranules.

(...)

11. Compositions as claimed in claim 7, wherein the active ingredient is selected from etoposide, calcium folinate, methotrexate, cyclophosphamide, procarbazine, fluorouracil, idarubicin, glypizide, glybenclamide, flutamide, nimesulide, piroxicam, ketoprofen, ibuprofen, gabapentin, 5-aminosalicylic, budesonide, metformin, mesalamine.

Como se puede apreciar, en esta anterioridad de nuevo se revela el uso de la técnica de granulado por fusión para la obtención de gránulos, en donde se hace mención explícita del uso de polietilenglicol en el proceso de fabricación y además se menciona la inclusión de gabapentina como principio activo de dichas formulaciones; con lo cual el nivel inventivo de lo reivindicado por la solicitud colombiana en trámite queda desvirtuado.

En conclusión, lo reivindicado por la solicitud colombiana en trámite se reduce a la aplicación de los conocimientos descritos con anterioridad en el estado de la técnica para un proceso de granulación ampliamente aplicado en la industria farmacéutica (melt granulation) y además, dicha técnica de granulación se encuentra igualmente descrita con anterioridad para el mismo principio activo (gabapentina) y con los mismos componentes (polietilenglicoles) que los que se reivindican en dicha solicitud colombiana; con lo cual es irrefutable la carencia al menos de nivel inventivo de la solicitud colombiana en cuestión.

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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 y 18 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 de las siguientes patentes: Patente americana US 3,263,006 publicada el 26 de Julio de 1966; Patente americana US 3,405,208 publicada el 08 de octubre de 1968; Patente americana US 3,601,847 publicada el 27 de octubre de 1969 y la Patente americana US 3,700,364 publicada el 24 de octubre de 1972.
- Abstracts de todas las publicaciones científicas mencionadas en el acápite de fundamentos de la oposición.
- La publicación internacional WO 03/035040 publicada el 1 de mayo de 2003, titulada "METHODS OF TREATMENT USING A GASTRIC RETAINED GABAPENTIN DOSAGE", páginas 1, 2, 14, 15.
- La publicación internacional WO 2003/068186 publicada el 21 de Agosto de 2003 y titulada "PHARMACEUTICAL FORMULATIONS AND SYSTEMS

FOR IMPROVED ABSORPTION AND MULTISTAGE RELEASE OF ACTIVE AGENTS" paginas 1, 19, 69, 74, 75, 80 y capítulo reivindicatorio.

- La publicación internacional WO 2003/002151 publicada el 09 de Enero de 2003 y titulada "ORAL PHARMACEUTICAL COMPOSITIONS WITH MODIFIED RELEASE OF THE ACTIVE INGREDIENT" capítulo reivindicatorio.

VII. ANEXOS

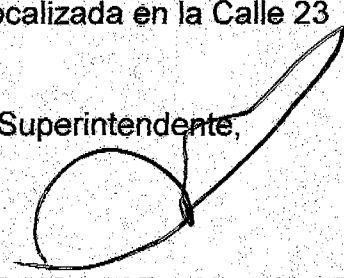
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

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 207, 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.

PROCESS FOR GRANULATING SUBSTANCES FROM THE MELT

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Filed July 31, 1962, Ser. No. 213,752

Claims priority, application Germany, Aug. 5, 1961,

F 34,617

13 Claims. (Cl. 264-8)

Substances forming plastic crystals and having a high vapor pressure, such as camphor, or having a low melting point, for example maleic anhydride, are difficult to granulate according to the usual methods, since in machines operating with great force, such as crushing rolls, the particles weld together and agglomerate. In high speed machines, such as hammer mills or disk attrition mills, relatively large amounts of cooling gas are passed through the machine causing considerable losses by evaporation on account of the high vapor pressure of the substance to be granulated. Furthermore, in all these machines contamination of the substance to be granulated can hardly be avoided, for example by lubricants or substances originating from the atmosphere.

It has now been found that substances can be granulated from the melt by allowing the molten mass to solidify in a container having elastically moldable walls, while the melt and the walls of the container are kept in continuous motion.

Substances which can be granulated by the process of the invention, shall not have too high a melting point (approximately below 250° C.) and they must not tend to form supercooled melts.

The process of the invention can be applied with special advantage to substances having a high vapor pressure, since evaporation losses can be avoided, and to substances having plastically soft crystals, for example camphor, since an agglomeration of the individual crystals is avoided.

The process of the invention is especially advantageous for granulating, for example, maleic anhydride, camphor, camphene, camphene, phthalic anhydride, naphthalene, dichloronaphthalene, fluorene, coumarin, menthol trioxane and p-dichlorobenzene.

As materials for the container having elastically moldable walls there can be used rubbers or plastic materials the softening or melting point of which is sufficiently above the temperature of the melt to be granulated, i.e. at least about 10° C. above that temperature. Materials of this kind are, for example, polyolefins such as polyethylene, polypropylene, polybutylene, mixtures thereof or copolymers of the corresponding monomers; polyhalogeno-olefins, such as polytetrafluoroethylene, polytrifluoroethylene; polyesters such as polyethylene glycol terephthalate; polyamides such as polyamides prepared on the basis of ϵ -caprolactam; plastics on the basis of homo- or copolymers of acrylonitrile or of a methacrylic acid ester; and plastics on the basis of cellulose. It is especially advantageous to use a material that is not wetted by the melt of the substance to be granulated.

If desired, the wall material can be reinforced, for example by glass fibers.

The granulation is preferably carried out at atmospheric pressure, but it is likewise possible to operate under elevated or reduced pressure. When selecting the wall material it must be taken into consideration that the atmospheric melting point of the substance to be granulated is displaced somewhat by changes in pressure.

In the simplest case, the process of the invention is

carried out in a manner such that the molten substance is put into a bag of a suitable plastic material and allowed to solidify while the bag is kneaded. Small crystals are formed which can neither deposit on the wall nor agglomerate on account of the motion, so that the substance is obtained at the end of the operation as a freely flowing powder.

The granulation is suitably carried out in a container which rotates around a horizontal axis or a slightly inclined axis, for example a rotary drum, of any desired rigid material (for example wood, metal or cardboard). In the container is arranged a bag of a suitable elastic material which is a little smaller than the container and up to one third of which is filled with the liquid substance to be granulated. The bag is subjected to a rotation together with the container.

An apparatus of this type has the further advantage that the granulation may be carried out with the exclusion of air in an atmosphere of a protective gas (for example nitrogen, carbon dioxide, hydrocarbon gases or noble gases). The substance solidifies in the bag to individual crystals which cannot agglomerate on account of their weight and the continuous motion, and cannot deposit on the walls of the container when the walls are not wetted by the substance. In this manner a flowable solid mass is obtained. By adjusting the cooling time and the number of revolutions, almost any desired grain size can be obtained. The speed of rotation of the container can vary within wide limits; it is preferably in the range of 2 to 100 revolutions per minute. The speed of rotation must be high enough that all agglomerating crystals are pulverized by the weight of the loose material, but it must not be so high that centrifugal forces occur which prevent the bag from falling down and inhibit the formation of granules.

For carrying out the granulation in continuous manner it is of advantage to use a tube which rotates around a horizontal axis or an axis deviating from the horizontal line by a small angle (up to 20° for example). In the tube a flexible hose of an elastically moldable material is arranged. The molten substance is continuously supplied at the upper end of the hose while the granules are continuously discharged at the lower end of the hose.

The apparatus is illustrated schematically in the accompanying drawing wherein:

FIGURE 1 is a view in elevation showing one embodiment;

FIGURE 2 is an end view taken on section line 2-2 of FIGURE 1; and

FIGURE 3 is a schematic view in elevation of another embodiment.

In the embodiment illustrated schematically in FIGURES 1 and 2, a tubular member 10 rotated on its axis by any suitable means such as rollers 11 is provided with a bag or the like 12 of yieldable material for containing a substance 14 that is initially molten and allowed to solidify while the tubular member 10 is rotated and the contents are thereby kneaded.

Referring now to FIGURE 3 of the drawing, a tubular member 20 positioned at an angle to the horizontal is shown mounted for rotation containing a bag or the like 22 communicating at one end with means for supplying a molten substance 24 to the bag, said means including a funnel member 26 and an axial member 27 and at the other end with a device for discharging the granulated substance from the granulating zone within the tubular member 20, said device including an axial member 29 and a funnel 30 for depositing the granulated substance into a receiver 31.

As compared with known processes, the granulation process of the invention offers the advantage that smaller

United States Patent Office

3,405,208

Patented Oct. 8, 1968

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3,405,208

METHOD FOR GRANULATING MELTABLE MATERIAL

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Continuation-in-part of abandoned application Ser. No. 444,120, Mar. 31, 1965. This application Dec. 12, 1966,
Ser. No. 600,938

Claims priority, application Japan, Apr. 7, 1964,
39/19,631

4 Claims. (Cl. 264-144)

ABSTRACT OF THE DISCLOSURE

A process for granulating meltable material employing vertical streams of a molten material by gravity and of immiscible liquid-freezant having a velocity equal to that of the stream of the molten material.

References to prior related applications

This is a continuation-in-part application of copending parent application Ser. No. 444,120 filed Mar. 31, 1965, now abandoned, and the priority dates to which the parent application is entitled are claimed for all subject matter common therewith.

The prior art

Paraffin wax is generally distributed in the form of thick plates or blocks. However, for many applications, granulated paraffin would be more desirable.

Summary of the invention

Therefore, the objects of the present invention are:

- to provide a granulating method especially suited to give a superior granulation of paraffin and similar meltable materials;
- to provide a granulating method for paraffin and similar meltable materials utilizing melting and subsequent freezing of the meltable material, said method yielding a superior product regardless of differences in the specific gravities of molten material and freezant;
- to provide a granulating method for paraffin and similar meltable materials yielding granules having an elongated shape.

Other objects and many of the attendant advantages of this invention will be readily appreciated as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings in which like reference numerals designate like parts throughout the figures thereof and wherein:

Description of the drawings

FIG. 1 is one example of the process of the invention. FIG. 2 is another example of the process of the invention.

Preferred embodiments of the invention

Briefly, the objects of the invention are achieved by merging liquid columns of freezant and molten material, freely falling at equal velocities; breaking the subsequently frozen column of molten material into elongated granules; and separating the granules from the freezant.

As applied herein, the term "freezant" is used analogously to the term "coolant" and refers to a cold liquid that solidifies molten material. A limitation on the freezant of the present invention is that it and the molten material must be immiscible.

FIG. 1 shows the merging of a falling stream 10 of

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molten paraffin with a falling stream 11 of freezant such as water into a unified stream 12. The water exits horizontally at 15° C. from pipe 13, while the paraffin exits horizontally at 80° C. from pipe 14. The pipes are at the same elevation. After the streams have left their respective pipes in a horizontal direction, their vertical component of velocity arises substantially due to gravitational acceleration. Since the streams are falling from the same elevation, physical principles show that the vertical velocities of the two streams are equal. Thus, when the two streams merge, as shown in FIG. 1, the relative velocity between the streams is zero. The freezant, depending on the particular conditions, encircles or adjoins the molten material and the two streams continue to flow downwards as a single stream.

After merging, the molten paraffin soon freezes into a solid column 15. This column is broken into elongated granules 16 by a conventional breaking means. The particular breaking means shown in FIG. 1 comprises four blocks 17 and a reciprocating rod 18. The directions of reciprocation are shown by the double-headed arrow a. As the rod reciprocates, it forces the solid column of paraffin against the blocks, thereby breaking it. The vertical separation of the blocks and the speed of reciprocation can be adjusted to regulate the length of the resulting elongated granules of paraffin.

Depending on the particular material being granulated, a breaking means may not be necessary. For example, in the case of paraffin, the unified stream coils in the basin 19, if a breaking means is not used. This coiled material can be put directly in a sales envelope. It shatters into short, needle-like pieces while it is being stuffed in.

In the example of FIG. 1, the water is collected in a basin 19. The upper level of the water is shown by line 20. Depending on the relative specific gravities of the meltable material and the freezant, the elongated granules will tend to sink or float in the basin. Following breaking, the granules are separated from the freezant by any conventional means. The particular means shown in FIG. 1 is a continuous belt 21 moving around guides 22. The belt has transverse bars 23. These bars scoop the granules from the freezant surface or from the depths of the basin. As the belt leaves the freezant collected in the basin, excess freezant drains back into the basin. Sieve holes in the belt and bars improve the draining. Finally, the granules are dumped into a stock pile.

In the examples of FIG. 1, the freezant is recirculated from the basin back to the pipe 13, via any conventional cooling means.

FIG. 1 shows a drying means to dry the water from the paraffin granules, before they reach the stock pile. This drying means can be any conventional means, such as a stream of dry air blowing across the path of the falling granules.

FIG. 1 shows a melting means for the meltable material.

Also shown in FIG. 1 are merging control means to assure that the freezant and molten material streams merge properly into one stream. For example, these control means can adjust the space between the two pipes, so that the streams merge approximately tangentially; or, the control means can control the pressures on the two streams as they leave the pipes, so that they merge approximately tangentially.

In FIG. 2, a modified example of the invention is shown. Here, pipe 14 conducts a stream 10 of molten paraffin into the center of a stream 11 of freezant. The stream of freezant 11 leaves the orifice 25 of the pipe 13 at the same location that the molten paraffin 10 leaves the orifice 26 of the pipe 14. The streams continue straight downwards as one united stream 12. First and second velocity con-

United States Patent

[11] 3,601,847

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99, Dzerzhinsk, all of, U.S.S.R.
[21] Appl. No. 869,512
[22] Filed Oct. 27, 1969
[45] Patented Aug. 31, 1971
[32] Priority Oct. 28, 1968
[33] U.S.S.R.
[31] 1281113

[50] Field of Search..... 18/2.4, 2.5
RR, 2.6, 2.7; 264/8, 13

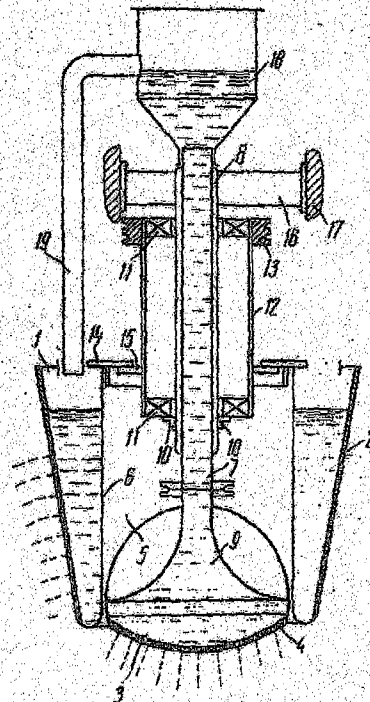
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Primary Examiner—J. Spencer Overholser
Assistant Examiner—R. L. Spicer, Jr.
Attorney—Waters, Roditi, Schwartz & Nissen

[54] DEVICE FOR GRANULATING MELTS
2 Claims, 2 Drawing Figs.

[52] U.S. Cl..... 18/2.6,
264/8, 264/13, 18/2.7
[51] Int. Cl..... B29c 5/04,
B29c 23/00, B22d 23/08

ABSTRACT: A device for granulating melts including a chamber with perforated lateral walls provided with a drive for rotating said chamber about its vertical axis and a stationary compartment with a perforated bottom mounted near the bottom of said chamber with perforated lateral walls in coaxial relationship with said chamber.



United States Patent

Vagin et al.

[15] 3,700,364

[45] Oct. 24, 1972

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141

[54] APPARATUS FOR GRANULATING MELTS

[72] Inventors: Alexei Alexeevich Vagin, Dzerzhinsk; Stanislav Valerievich Yablonsky, Kazan; Pete Stepanovich Voloshin, Dzerzhinsk; Nikolai Gregorievich Sharov, Dzerzhinsk; Viktor Ivanovich Shiborin, Dzerzhinsk; Vladimir Efimovich Novakowsky, Dzerzhinsk; Grigory Vasilievich Kolpakov, Dzerzhinsk; Mark Efremovich Ivanov, Moscow; Viktor Mikhailovich Lindin, Moscow; Danil Yakovlevich Lipsky, Moscow, all of U.S.S.R.

[73] Assignee: Dzerzhinsky Filial Nauchno-Issledovatel'skogo i Konstrukorskogo Instituta Khimicheskogo Mashinostroenia, Dzerzhinsk, U.S.S.R.

[22] Filed: Dec. 23, 1969

[21] Appl. No.: 887,640

[30] Foreign Application Priority Data

Dec. 23, 1968 U.S.S.R.1291391

[52] U.S. Cl.425/7, 264/13, 425/73, 425/104

[51] Int. Cl.B22d 23/08, B29c 23/00

[58] Field of Search.....18/2.5 R, 2.7, 2.4, 2.5 RR, 18/1 A, 1 B, 264/13

[56] References Cited

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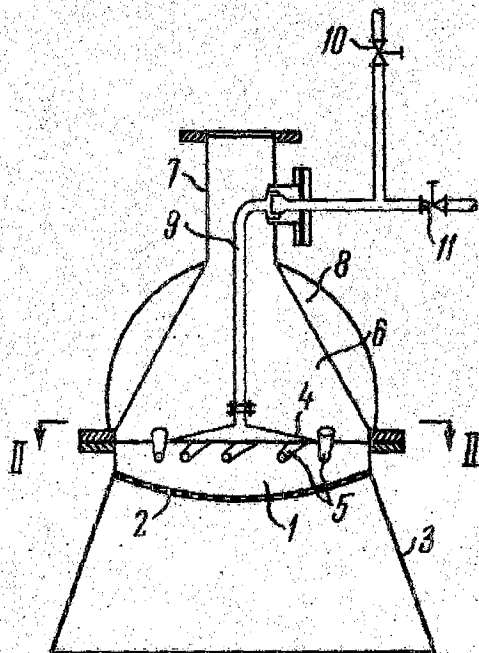
Primary Examiner—Robert L. Spicer, Jr.

Attorney—Waters, Roditi, Schwartz & Nissen

[57] ABSTRACT

An apparatus for granulating melts comprising a chamber with a perforated bottom provided with branch pipes for supplying the melt into this chamber, in which the outlet tips of the branch pipes are directed relative to the perforated bottom so as to provide a continuous rotary motion of the melt above the inner surface of the bottom.

5 Claims, 4 Drawing Figures



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TTT
15

Effect of Crystallization Behavior of Polyethylene Glycol 6000 on the Properties of Granules Prepared by Fluidized Hot-Melt Granulation (FHMG)

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The objective of this study was to investigate the effect of the crystallization behavior of Macrogol 6000 (polyethylene glycol 6000; PEG 6000), used as a binder, during the solidification process on the properties of mononucleic granules prepared by the fluidized hot-melt granulation (FHMG) technique. Crystallization of PEG 6000 from molten liquid was investigated using differential scanning calorimetry (DSC) and hot stage microscopy. The results obtained from the measurement of isothermal crystallization demonstrated that crystallization of PEG 6000 was either slow or rapid. Analysis based on solid-state decomposition showed that slow crystallization was due to the two-dimensional growth of nuclei mechanism, while rapid crystallization was due to the three-dimensional growth of nuclei mechanism. Observation of the crystallization of PEG 6000 by hot stage microscopy supported the existence of two different crystallization mechanisms. Granules containing PEG 6000 that underwent rapid crystallization during FHMG showed a significantly higher fraction powder under 150 μm in diameter. This was caused by the loss of powder particles from the surface of mononucleic granules during the solidification process, because many cracks were observed after crystallization of PEG 6000 with a short isothermal crystallization time (ICT) due to the reduced sticking of particles. The results of this study suggested that the crystallization behavior of the binder during the solidification process of FHMG can influence the properties of the resultant granules, such as particle size distribution, content uniformity or taste masking. It was also indicated that measuring the ICT using DSC was a useful method to classify PEG 6000.

Key words polyethylene glycol 6000; fluidized hot-melt granulation; crystallization; granules

Granulation is one of the most important processes in pharmaceutical manufacturing. Powders show improved flowability and content uniformity as a result of granulation. Hot-melt granulation (HMG), using meltable materials as thermal binders, is classified as a dry granulation method. HMG is a well-known granulation technique that utilizes adhesion due to the melting or softening of materials that are heated to near or above their melting point.¹⁾ Currently, HMG is of great interest in the pharmaceutical field, since granules may be prepared simply without using solvents or water. HMG is also a very useful method for granulating and stabilizing drugs that are susceptible to hydrolysis.²⁾ Ukita and Murakami demonstrated that melt granulation prevented the vaporization of essential oils during the granulation process because the melted material covered the surface of the granules.³⁾ The melt granulation process can also be applied to prepare sustained-release dosage forms of drugs. Maejima *et al.* developed the tumbling melt granulation (TMG) technique, which is a type of powder coating method using hydrophobic melting materials for the production of sustained-release beads.^{4–6)} Faham *et al.* investigated hot-melt coating technology using a spray system.⁷⁾ In addition, this technique has advantages for scaling-up and process validation because there are only a few controlling parameters.⁸⁾

Conventional HMG is performed in a high shear mixer or a tumbling mixer with almost 30 w/w% of low melting point material and other powder excipients. As a result, granules prepared by the HMG method are dense and very hard, having a sand-like feeling. Therefore, this method was not thought to be good for making preparations of granules and fine granules as defined by the Japanese Pharmacopoeia XIV.

On the other hand, we have developed fluidized hot-melt

granulation (FHMG), a novel, simple, and useful method of preparing granules without using solvents or water.^{9–12)} This technique is also easily controlled, so we have investigated its usefulness in the field of pharmaceutical formulation and production technology.⁹⁾ In general, fluidized bed granulation is a suitable method to prepare fine granules as well as granules for tabletting, because the lack of any shear force during granulation results in porous granules with a low strength.^{13,14)} Our studies have also shown that granules prepared by the FHMG method are softer compared with those obtained by the conventional HMG method. In previous studies, FHMG has been shown to have the capability to make fine, taste-masked granules containing a bitter drug substance,¹¹⁾ as well as being useful for making granules for tabletting.¹⁵⁾ Schaefer *et al.* studied the effect of process^{16,17)} and formulation variables^{18–20)} on melt granulation with low molecular weight PEGs using a high shear mixer. Voimovich *et al.* also investigated the effect of the apparatus and the process variables during melt pelletization using a high shear mixer.²¹⁾ Haramishi *et al.* reported a formulation study and the mechanism of obtaining mononucleic granules with a high yield by FHMG.⁹⁾ However, most studies have concentrated on formulation and have been performed to investigate the granulation mechanism or the optimum conditions. Thus, few reports have described the solidification process of melting materials during HMG.

The objective of the present study was to investigate the effect of the crystallization behavior of Macrogol 6000 (polyethylene glycol 6000; PEG 6000), which is used as a binder, during the solidification process on the properties of mononucleic granules prepared by a FHMG. The crystallization behavior of PEG 6000 from molten liquid was investi-

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gated using differential scanning calorimetry (DSC) and hot stage microscopy. The process of isothermal crystallization was analyzed by a solid-state decomposition method.^{22,23} Granules produced by the FHMG technique were also evaluated.

Experimental

Materials Macrogl 6000 (polyethylene glycol 6000; PEG 6000, NOF Corp., Tokyo, Japan) was of JP grade. PEG 6000 was pulverized by a sample mill, and then sieved. The fraction obtained between the 180 μm and 250 μm screens was used for granulation. Cetrazate hydrochloride (CET, Daiichi Pharm. Co., Ltd.) was used as a model drug. α -Lactose monohydrate 450 mesh (Pharmatose 450M) was purchased from DMV (Veghel, The Netherlands). The other materials used were corn starch (Nihon Shokuhin Kako Co. Ltd., Tokyo, Japan) and talc (Matsumura Sangyo Co. Ltd., Osaka, Japan).

Methods FHMG Granules were prepared by the FHMG technique using a fluidized-bed system (FLO-1, Freund Industrial Co. Ltd., Tokyo, Japan). Table 1 shows the formulations employed for FHMG. The content of PEG 6000 as a binder was fixed at 25 w/w % and its particle size was 180–250 μm . PEG 6000 and the other powders were added to the fluidized-bed, and then the inlet temperature and the shaking/interval time were set at 85 °C and 2 s/15 s, respectively. The air flow rate was adjusted to 1 m/s. The powders were heated and held for 10 min when the powder bed temperature reached 55 °C, after which the powders were cooled to 40 °C.

Measurement of the Size Distribution and the Mean Diameter of Granules Prepared by FHMG Sieve analysis was carried out using a rotap shaker (Rida Selsakusyo Co. Ltd., Osaka, Japan). Granules were sieved with 150, 180, 250, 355, and 500 μm sieves. Then the size distribution and the mean diameter of the granules were calculated from the log-normal distribution equation.

Characterization of PEG 6000 The solidifying temperature of PEG 6000 was determined by using a differential scanning calorimeter (DSC-7, Perkin-Elmer Corp., CT, U.S.A.). The instrument was calibrated with an indium standard before measurement. Approximately 10 mg samples were weighed and sealed in aluminum pans. The samples were heated to 80 °C and cooled to -20 °C at a rate of 10 °C/min. Scanning was done under a nitrogen purge at a heating rate of 5 °C/min.

The viscosity of molten liquid PEG 6000 was measured at 98.89 °C (210 F) by using a Cannon-Fenske viscometer according to the IIS K-2263 method. PEG 400 was used as the outer medium.

The mean molecular weight of PEG 6000 was measured by the gel per-

meation chromatography (GPC) method (column: TSK gel G 6000 PW_{XL} + G 3000 PW_{XL}, 7.8 mm i.d. $\times$ 60 cm, column temperature: 40 °C, mobile phase: 50 mmol/L NaCl, flow rate: 1.0 ml/min, injection volume: 200 μL).

PEG 6000 (3 g) was dissolved in 100 ml of purified water, and then the pH was determined with a pH meter.

Isothermal Crystallization of PEG 6000 DSC (DSC-7, Perkin-Elmer Corp., CT, U.S.A.) was used to investigate the isothermal crystallization behavior of molten PEG 6000. Approximately 10 mg samples were weighed and sealed in aluminum pans. In order to crystallize PEG 6000 at the target temperature under the supercooling state as correctly as possible, the samples were heated and held at 80 °C for 5 min, and then were flash cooled to 40, 43, and 45 °C at a cooling rate of -200 °C/min using liquid nitrogen. Isothermal crystallization was done each temperature and the process of crystallization was analyzed by the Hancock-Sharp method.²⁰ The most common and widely applicable kinetic equation for solid-state decomposition was described by Avrami-Erofeev²² as follows:

$$\alpha = 1 - \exp(-Bt^m) \quad (1)$$

where α is the ratio of transition at time t , B is the constant, and m is the intrinsic value obtained from the theoretical equation for solid-state decomposition. α was determined by measuring the area under the crystallization peak of DSC profile at each temperature. Equation 1 can be written as

$$\ln[-\ln(1-\alpha)] = \ln B + m \cdot \ln t \quad (\alpha = 0.15-0.5) \quad (2)$$

When the slope m is calculated from the plot of $\ln[-\ln(1-\alpha)]$ versus $\ln t$, the mechanism of solid-state decomposition can be classified by referring to Table 2. The isothermal crystallization time (ICT) was defined as the time for complete solidification and was determined from the DSC profile.

Hot Stage Microscopy To observe its crystallization behavior, molten PEG 6000 was monitored and recorded using a hot stage microscopy system (FP84HT, Mettler Toledo, Switzerland) with a polarized filter. Molten PEG 6000 was cooled at a rate of -2 °C/min by controlling the temperature of the hot stage.

Powder X-Ray Diffraction (XRD) A powder X-ray diffractometer (MXP-3, MAC Science, Tokyo, Japan) was used to characterize the crystalline properties of PEG 6000. Samples were exposed to Cu-K α radiation under 35 kV and 20 mA over the 2θ range from 10° to 40° at increments of 2°/min.

Scanning Electron Microscopy (SEM) Granules were mounted on SEM sample stubs using double-faced adhesive tape and were coated with gold-palladium. Observation was carried out at a voltage of 15 kV on an SEM instrument (JSM-5600LV, JEOL Ltd., Tokyo, Japan).

Table 1. Formulations Used for Fluidized Hot-Melt Granulation (FHMG)

Component	Composition (%)		Remarks
Cetrazate hydrochloride	60		Mean diameter: 20 μm
Lactose		60	DMV 450M
Polyethylene glycol 6000	25	25	PEG 6000, 180–250 μm fraction
Corn starch	13	13	
Talc	2	2	
Total	100	100	

Table 2. Kinetic Equations and Values of m for the Most Common Mechanisms of Solid-State Decomposition

Symbol	Equation	m	Mechanism
R_1	$\alpha = kt$	1.24	Zero-order mechanism (Polanyi-Winger equation)
R_2	$1 - (1 - \alpha)^{1/2} = kt$	1.11	Phase boundary reaction, cylindrical symmetry
R_3	$1 - (1 - \alpha)^{1/3} = kt$	1.07	Phase boundary reaction, spherical symmetry
F_1	$-\ln(1 - \alpha) = kt$	1.00	Random nucleation, one nucleus on each particle
A_2	$[-\ln(1 - \alpha)]^{1/2} = kt$	2.00	Random nucleation, two-dimensional growth of nuclei (Avrami-Erofeev equation)
A_3	$[-\ln(1 - \alpha)]^{1/3} = kt$	3.00	Random nucleation, three-dimensional growth of nuclei (Avrami-Erofeev equation)
D_1	$\alpha^2 = kt$	0.62	One-dimensional diffusion
D_2	$(1 - \alpha) \cdot \ln(1 - \alpha) + \alpha = kt$	0.57	Two-dimensional diffusion
D_3	$[1 - (1 - \alpha)^{2/3}]^2 = kt$	0.54	Three-dimensional diffusion (Jander equation)
D_4	$(1 - 2\alpha/3) \cdot (1 - \alpha)^{2/3} = kt$	0.57	Three-dimensional diffusion (Ginstling-Brounstein equation)

$$a) \ln[-\ln(1-\alpha)] = \ln B + m \cdot \ln t \quad (\alpha = 0.15-0.50)$$

Table 3. Characteristics of PEG 6000

Lot	Solidifying temperature (°C)	Mean diameter (μm)		OH-value	Mean molecular weight	Viscosity (mm ² /s)	pH
		D ₅₀	σg				
A	58.1	200	1.1	12.6	8905	810.8	7.3
B	57.9	192	1.2	12.5	8976	802.1	7.2
C	58.6	197	1.2	12.4	9048	827.0	7.1
D	58.2	200	1.1	12.5	8976	826.4	7.2
E	58.1	191	1.1	12.5	8976	801.4	7.1
F	58.0	193	1.1	13.1	8585	793.6	7.2

Results and Discussion

FHMG FHMG is recognized as a novel and a simple method of making granules with a small size distribution. Haramiishi *et al.* investigated the formulation and mechanism of FHMG.²¹ They reported that there was an optimum ratio between the powder and the melting material to obtain mononucleic particles by FHMG, which was related to the specific surface area and weight.²¹ In this study, PEG 6000 was fixed at the optimum amount of 25 w/w % to obtain the highest yield of fine granules and the lowest amount of 150 μm pass (%). The other materials used, apart from PEG 6000, were all from the same lots to avoid inter-lot variations.

Various characteristics of the six lots of PEG 6000 used in this study are summarized in Table 3. No marked inter-lot differences of physical properties were observed. There were also no significant differences of the powder X-ray diffraction patterns of PEG 6000. After FHMG was done using CET as the active drug, however, a marked difference in the amount of 150 μm pass (%) was observed (Fig. 1). The content of CET under 150 μm was approximately 145% of the ideal amount, which means the labeled amount of CET/g. Lots A and B showed a smaller fine particle fraction compared with lots of C, D, E, and F. When lactose with the same mean diameter was used instead of CET, almost the same tendency of the amounts of particles under 150 μm (%) were obtained, as shown in Fig. 1. When the heating and cooling processes during granulation were observed in detail, it was found that fine powder was generated during the solidification process. Since no significant inter-lot differences of the physicochemical properties of PEG 6000 were observed, we focused on the solidification of PEG 6000. Using DSC, Larhrib and Wells demonstrated differences in the compression properties of PEG 10000 after thermal treatment.²⁴ Therefore, to clarify the influence of differences between lots of PEG 6000, the solidifying properties of each lot were evaluated by using DSC.

Characteristics of PEG 6000 Generally, it is known that a supercooling phenomenon will be observed during the solidification of polymers like PEG 6000 and this phenomenon was observed for molten PEG 6000. To clarify the solidification properties of PEG 6000, isothermal crystallization was investigated by DSC at a cooling rate of -200 °C/min. Figure 2 shows the isothermal crystallization profile of Lot B, which yielded the smallest amount of fine particles (150 μm pass). When the isothermal crystallization temperature was set at 40, 43 and 45 °C, the ICT was 0.7 min, 1.7 min, and 3.0 min, respectively. As the isothermal crystallization temperature became higher, the ICT tended to become

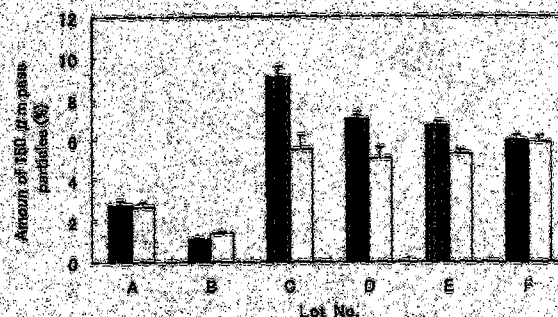


Fig. 1. Amount of 150 μm Pass Particles (%) in Granules Made with a Different Lots of PEG 6000 (*n*=3)

■: CET, □: lactose

longer. On the other hand, the isothermal crystallization profile of Lot C, which yielded the largest amount of fine particles (150 μm pass), is shown in Fig. 3. At every isothermal crystallization temperature, PEG 6000 was rapidly crystallized and the ICT was under 1 min. From these results, it was found that Lots C, D, E, and F of PEG 6000, which yielded relatively large amounts of 150 μm pass (%) after FHMG, had considerably shorter ICTs than Lots A and B during isothermal crystallization. Table 4 shows a comparison of the lots classified by slow or rapid crystallization. However, no marked differences of the physicochemical parameters were observed.

The heat of fusion (ΔH) during isothermal crystallization at 40, 43, and 45 °C was investigated for each lot of PEG 6000. Lots A and B were defined as showing slow crystallization, whereas Lots C, D, E, and F were defined as showing rapid crystallization. A summary of the ΔH values of PEG 6000 during isothermal crystallization is shown in Table 5. No significant difference of ΔH values was observed between PEG 6000 lots showing slow or rapid crystallization. These results were consistent with the X-ray diffraction patterns of the PEG 6000 lots before melting and after crystallization. It was concluded that the crystalline form of PEG 6000 was the same for slow and rapid crystallization.

The crystallization process of PEG 6000 under isothermal conditions were analyzed by the Hancock-Sharp method,²³ which can be applied to understand the transition of polymorphic forms²⁵ or crystallization.²⁶ With this method, the slope *m* estimated by plotting $\ln[-\ln(1-\alpha)]$ against $\ln t$ according to Eq. 2 is used in order to distinguish the reaction mechanism:

$$\ln[-\ln(1-\alpha)] = \ln B + m \cdot \ln t \quad (2)$$

where α is the fraction of transition and *B* is a constant. The

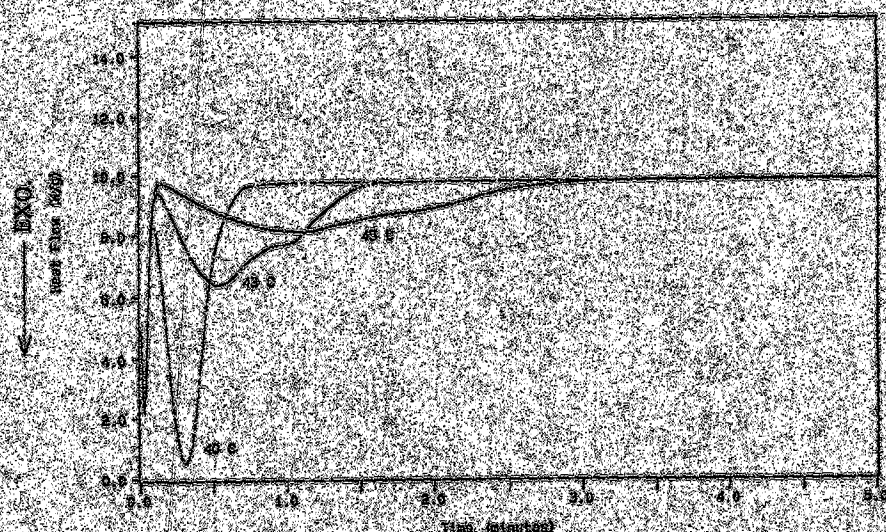


Fig. 2. Isothermal Crystallization Curves of PEG 6000 at 40, 43, and 45 °C
Lot B, cooling rate $\sim 200^\circ\text{C/min}$

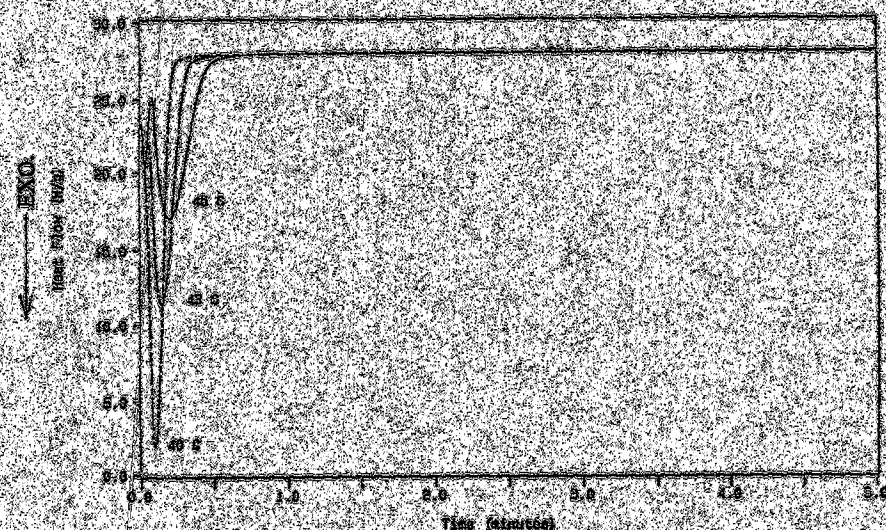


Fig. 3. Isothermal Crystallization Curves of PEG 6000 at 40, 43, and 45 °C
Lot C, cooling rate $\sim 200^\circ\text{C/min}$

Table A. Characteristics of PEG 6000 Showing Slow or Rapid Crystallization

Classification	Lot	Solidifying temp. (°C)	Mean diameter (μm)		OH-value	Mean molecular weight	Viscosity ($\text{mPa}\cdot\text{s}$)	pH
			D_{50}	σ_g				
Slow	A, B	58.0 ± 0.1	193.0 ± 4.4	1.1 ± 0.1	12.7 ± 0.3	8615 ± 220	802.2 ± 8.6	7.2 ± 0.1
Rapid	C-F	58.3 ± 0.3	196.0 ± 4.6	1.1 ± 0.1	12.5 ± 0.1	8600 ± 42	818.3 ± 14.6	7.1 ± 0.1

value of m is an intrinsic value determined from various theoretical equations for solid-state decomposition. The results for Lot B (slow crystallization) and Lot C (rapid crystallization) are shown in Figs. 4 and 5, respectively. Every plot showed good linearity. The Hancock-Sharp constant (m) of PEG 6000 lots with slow and rapid ICT was calculated by the least-squares method. The results suggested that PEG 6000 showing slow crystallization had an m value of 2.9 ± 0.4 and occurred by the mechanism of three-dimensional growth of

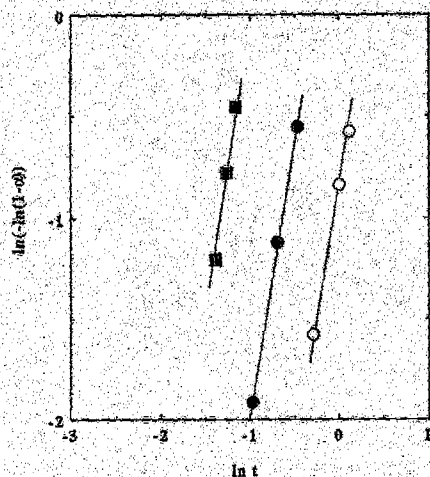
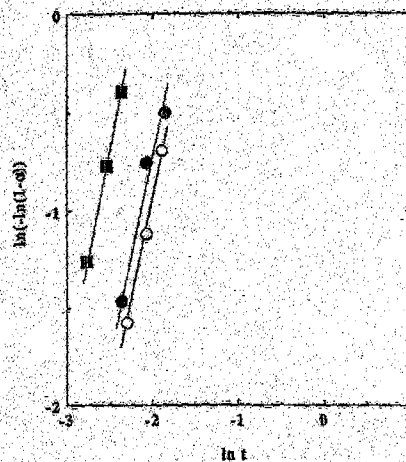
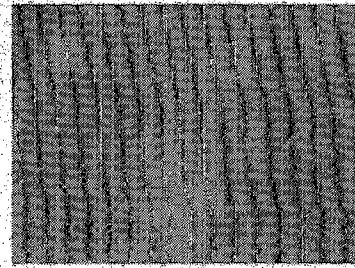
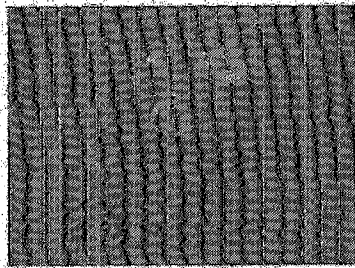
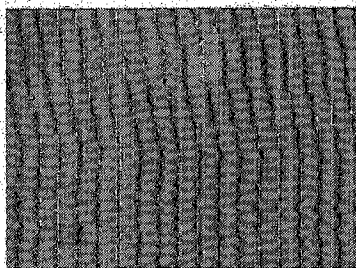
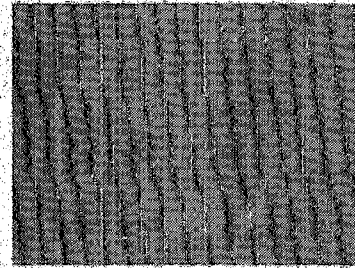
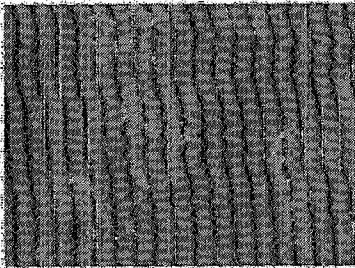
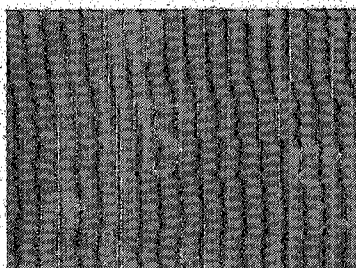
nuclei (A_3). On the other hand, the m value of PEG 6000 showing rapid crystallization was 2.1 ± 0.1 , indicating that crystallization followed the mechanism of the two-dimensional growth of nuclei (A_2).

Morphological observation of PEG 6000 during crystallization was also done. To observe crystallization behavior, molten PEG 6000 was monitored and recorded by using a hot stage microscopy system with a polarized filter. Figure 6a shows the crystallization of Lot B from a temperature of 48.5

Table 5. Heat of Fusion (ΔH) of PEG 6000 Obtained from Isothermal Crystallization

Classification	Lot	ΔH (J/g) (Mean $\pm$ S.D.)		
		40 °C	43 °C	45 °C
Slow	A, B	168 $\pm$ 7	166 $\pm$ 4	161 $\pm$ 4
Rapid	C—F	172 $\pm$ 8	168 $\pm$ 7	167 $\pm$ 4

to 42.9 °C. At 48.5 °C, only one crystal nucleus was seen in the field of view, and it was recognized that the nucleus grew slowly to form a large crystal. On the other hand, many nuclei were observed in the sample of Lot C at the same temperature at 48.5 °C, and many small crystals were seen in the field of view (Fig. 6b). At the end of the crystallization process at 42.9 °C, many cracks between crystals were observed due to the effect of crystal growth. It was thought that the amount of fine particles under 150 μ m was determined at the time of solidification during FHMg because of the creation of cracks between PEG 6000 crystals.

Fig. 4. Hancock-Sharp Plots for Isothermal Crystallization of PEG 6000 ($\alpha=0.15\sim0.50$)Lot: B, C; 45 °C ($r=0.999$), 43 °C ($r=0.999$), 40 °C ($r=0.998$).Fig. 5. Hancock-Sharp Plots for Isothermal Crystallization of PEG 6000 ($\alpha=0.15\sim0.50$)Lot: C; 45 °C ($r=0.998$), 43 °C ($r=0.966$), 40 °C ($r=0.999$).(a) Lot: B ($\times 100$)(b) Lot: C ($\times 100$)Fig. 6. Photo Micrographs of PEG 6000 during Crystallization (Magnification: $\times 100$)

Each number in the photo shows the temperature at that time. (a) Lot: B, (b) Lot: C.

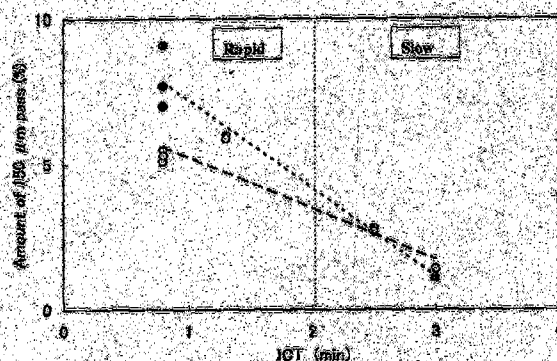


Fig. 7. Effect of the ICT of PEG 6000 at 45 °C on the Amount of 150 μ m Pass Particles (%) after FHMg

●: CET, ○: lactose. Lots of PEG 6000 are the same as those in Table 3.

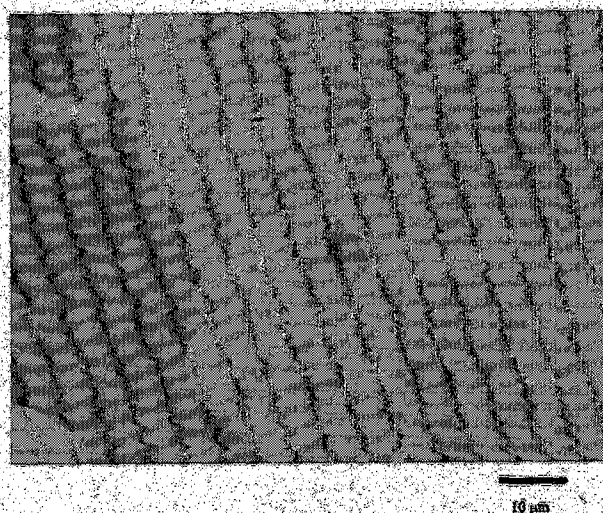


Fig. 8. SEM Photograph of Granules Having the Crack on the Surface Prepared by FHMg Containing PEG 6000 (Lot C, Magnification: $\times 1500$)

Effect of Crystallization on the Properties of Granules
Based on the results obtained above, the relationship between the ICT and the amount of 150 μ m pass (%) after FHMg using PEG 6000 is summarized in Fig. 7. It is obvious that the ICT of PEG 6000 affects the amount of fine particles after FHMg, since Lots A and B with a long ICT yielded fewer such particles compared with lots having a short ICT when using both CET and lactose as actives. When the amount of 150 μ m pass (%) was plotted against the ICT of PEG 6000, a good correlation was observed using both CET and lactose (Fig. 7). Therefore, prediction of the amount of 150 μ m pass (%) is possible by measuring the ICTs for CET and lactose. Moreover, PEG 6000 with an ICT of more than 2 min is preferable for FHMg. Generally, it is recognized that fewer fine particles is an advantage for taste masking coating or for packaging processes.

The morphological feature of granules obtained by FHMg were investigated using SEM. Figure 8 shows the surface of the granules containing Lot C. The crack on the surface of the granules is observed.

Thermodynamically, crystallization rate becomes larger when the difference of the free energy of PEG 6000 between the phases of the molten liquid and the crystalline caused by

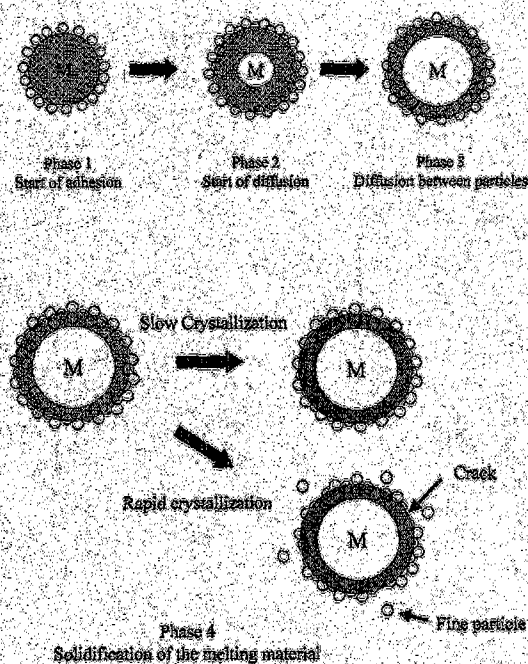


Fig. 9. Schematic Representation of the Mechanism of Fine Powder Generation from Mononucleic Granules during FHMg Method

M: Melting material.

the phase separation during the crystallization process increases. Therefore crystallization rate became larger when nuclei generated more, and ICT was considered to be shorter because of the two-dimensional growth of nuclei mechanism.

On the other hand, crystallization rate became smaller when nuclei generated fewer, and ICT was considered to be longer because of the three-dimensional growth of nuclei mechanism. After crystallization, cracks between the crystalline of PEG 6000 were generated more along with the discontinuous planes when crystallization rate was larger, since nuclei generated more.

From these results, the difference in the crystallization mechanism of PEG 6000 influenced the generation of the crack on the surface of the granules. Anti-adhesion of powder occurred at the point of crack during the crystallization of PEG 6000, and the amount of particle under 150 μ m could be influenced.

A schematic representation of the mechanism of fine powder generation from mononucleic granules during FHMg is shown in Fig. 9. In phase 1, the meltable material (such as PEG 6000) begins to melt and an adhesion force acting on the particles is generated. In phase 2, the meltable material starts to diffuse between the powders adhering to its surface when the temperature exceeds its melting point. The molten material is diffused and spreads between the particles in phase 3. After heating, the granules are cooled below the solidifying temperature of the meltable material in phase 4. During solidification of the granules, the meltable material is crystallized. When the meltable material has a long ICT, powder adheres to the surface strongly during the crystallization process. However, if the meltable material has a short ICT, the powder does not adhere so well during cooling process of FHMg, since many cracks between PEG 6000 are generated on the surface of the granules after crystallization

due to the reduced sticking of particles on the surface of mononucleic granules.

Conclusions

The effect of the crystallization properties of PEG 6000 (used as a melting material) on mononucleic granules prepared by a novel FHMG method was investigated. It was found that PEG 6000 has two different crystallization mechanisms, one being two-dimensional growth of nuclei mechanism (A_2), the other being three-dimensional growth of nuclei mechanism (A_3). The amount of small particles (150 μ m pass) in the granules showed a decrease with the increase of ICT. This indicates that a short ICT of PEG 6000 depending on its crystallization behavior may strongly affect on the particle size distribution and lead to decreased taste masking of granules. Therefore, the crystallization behavior of PEG 6000 for used in FHMG should be monitored. To reduce the amount of fine particle after FHMG, PEG 6000 having an ICT of more than 2 min at 45 °C should be used.

The results of this study also indicate that FHMG is a simple and a useful method of preparing granules without the need for solvents or water. However, the crystallization behavior of the melting material should be taken into account carefully.

Generally, it is well known that existence of a very small amount of impurities, or an addition of some ingredient, affects on the generation of crystal nuclei. However, it is still unclear what affects the crystallization behavior of PEG 6000. To identify the factors that modulate crystallization of PEG 6000, further studies are necessary.

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Related Subject CHALCOGENIDES; INDUSTRY; NATIONAL ORGANIZATIONS; NORTH AMERICA; OXIDES; OXYGEN COMPOUNDS; PHOSPHORUS COMPOUNDS; US ORGANIZATIONS

Description/Abstract Melt-type processes developed by TVA, in which wet-process phosphoric acid provides all or most of the P/sub 2/O/sub 5/ in granular fertilizers, show promise in decreasing fuel, total energy, investment, and operating cost. The analyses and estimates were based on pilot-plant studies and demonstration-plant experience at TVA's National Fertilizer Development Center, Muscle Shoals, Alabama. It is shown that elimination of fuel for drying and substantially decreased horsepower requirements (particularly in a new plant) would decrease energy requirement in the granulation plant by about 1,000,000 Btu's per metric ton of P/sub 2/O/sub 5/. When coupled with lower operating costs that are based on investment factors, the savings for the granulation plant is indicated to be about \$6 per metric ton of P/sub 2/O/sub 5/ for a melt-type ammonium phosphate plant. As explained in the text, there would be just about a tradeoff in energy required for drying in a conventional ammonium phosphate granulation plant (where wet-process acid also is produced) against the equivalent steam that would be needed to concentrate the feed acid from 40% P/sub 2/O/sub 5/ to 52 to 54% P/sub 2/O/sub 5/ for use in melt-type granulation. This would decrease the overall estimated savings for a melt-type ammonium phosphate granulation plant to about \$3.65 per metric ton P/sub 2/O/sub 5/. In the case of NPK granulation plants using 52 to 54% P/sub 2/O/sub 5/ acid shipped in, the full indicated savings of about \$5.10 per metric ton nutrient should be realized. Savings in existing and new plants are indicated.

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Alternative Granulation Technique: Melt Granulation

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Abstract

A melt granulation process has been investigated (1, 2) which efficiently agglomerates pharmaceutical powders for use in both immediate- and sustained-release solid dosage forms. The process utilizes materials that are effective as granulating fluids when they are in the molten state. Cooling of the agglomerated powders and the resultant solidification of the molten materials completes the granulation process. Both the molten agglomeration and cooling solidification were accomplished in a high shear Collette Grai mixer equipped with a jacketed bowl. Hence, the melt granulation process replaces the conventional granulation and drying operations which use water or alcohol solutions. The melt granulation process has been investigated using immediate- and sustained-release TAVIST® (clemastine fumarate USP) tablet formulations. The TAVIST granulations have been characterized by power consumption monitoring, measurement of the granulation particle size distribution, bulk and tapped density determinations, and loss-on-drying measurements. Scale-up of the melt granulation process for the sustained release TAVIST tablet formulation was judged successful based on a comparison of the hardness, friability, weight uniformity during compression, disintegration time, and dissolution rate data obtained at different manufacturing scales.

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Melt Granulation in A Laboratory Scale High Shear Mixer

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Abstract

The applicability of a 10 litre high shear mixer for melt granulation of dicalcium phosphate and lactose is examined. Polyethylene glycol (PEG) 3000 and 6000 were used as melting binders in concentrations of 15-20% w/w. The effects of binder concentration, massing time, impeller speed, and particle size of the PEG 6000 on granule size, granule size distribution and intragranular porosity are investigated.

It is shown that pellets of a narrow size distribution can be produced by the use of a high impeller speed. Granule size and size distribution are markedly influenced by binder concentration and massing time. The particle size of the PEG has only a minor effect on the granule growth. Granule growth mechanisms by melt granulation are discussed on the basis of the liquid saturations and the amounts of binder liquid and are compared with previous results on wet granulation.

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The aim of this study was to prepare, by melt granulation, granules containing ibuprofen as a poorly water soluble model drug in order to improve its dissolution rate and its availability; lactose as a diluent and poloxamer 188 (Lutrol F68), as a new meltable hydrophilic binder, were used. The granules were prepared in a laboratory-scale high-shear mixer, using a jacket temperature of 50 degrees C and an impeller speed of 500 rpm. The particle size analysis shows that the main fraction was between 200 and 500 microm, while the determination of drug content indicated that ibuprofen was quite uniformly distributed in all the fractions. Scanning Electron Microscopy (SEM), image and fractal analysis revealed that the granules did not have a perfect spherical shape and a rugged surface ($D(s)=2.6475$). The in vitro dissolution tests showed an increase in the dissolution rate of granules compared to pure drug and physical mixture. The characterisation of the samples, performed by Differential Scanning Calorimetry (DSC) and X-ray powder diffraction (XRD), suggests that the improvement of dissolution rate could be correlated to the formation of a eutectic mixture between the drug and the binder. Stability studies indicated that the granule properties do not change, at least after 1 year of storage at 25 degrees C. In conclusion, the results of this work suggest that the melt granulation technique is an easy and fast method to improve the dissolution rate of ibuprofen, using poloxamer 188 as a new hydrophilic meltable binder.

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Ibuprofen (Advil® Caplets®, Advil® Children's, Advil® Gel Caplets, ...) Prescription ibuprofen is used to relieve pain, tenderness, swelling, and stiffness caused by osteoarthritis (arthritis caused by a breakdown of the lining of the joints) and rheumatoid arthritis (arthritis caused by auto...

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The Control of Drug Release from Conventional Melt Granulation Matrices

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Abstract

Sustained release potassium chloride tablets were prepared using a melt granulation formulation in a Baker Perkins Granulator. Parts of the validation for this manufacturing process are highlighted in this paper including granulation end point temperature, incorporation of extragranular excipients, amount of wax in the formulation, granule cooling rate and scale of the operation. A number of other factors have been studied which are not included here although they are no less important. The release of potassium chloride from tablets was found to be dependent on the wax level and the amount of extragranular excipients ("wicking agent"). Within the controlled production process, any variation in granulation end point temperature and granule cooling rate should not have any significant effect.

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(54) Title: **METHODS OF TREATMENT USING A GASTRIC RETAINED GABAPENTIN DOSAGE**

(57) Abstract: A method of treatment for epilepsy and other disease states is described, which comprises the delivery of gabapentin in a gastric retained dosage form.

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METHODS OF TREATMENT USING A GASTRIC RETAINED GABAPENTIN
DOSAGE

Background Of The Invention

5 **Technical Field**

The present invention relates to the use of gabapentin in a gastric retained dosage form. More specifically, the invention relates to the use of such dosage form to treat epilepsy and other disease states.

10 **Background**

Gabapentin (1-(aminomethyl)cyclohexanecarboxylic acid) is an anti-epileptic drug that is currently available in 100 mg, 300 mg and 400 mg hard shell capsule as well as 600 mg and 800 mg tablet dosage forms, with recommended dosing of 900 mg to 1800 mg total daily dose in three divided dosages. The oral bioavailability is dose-dependent, with approximately 60% bioavailability for a dose in the range of 300-400 mg, but with only 35% bioavailability for a dose of 1600 mg (Bourgeois, *Epilepsia* 36 (Suppl. 5):S1-S7 (1995); Gram, *Epilepsia* 37 (Suppl. 6):S12-S16 (1996)). The decrease in bioavailability with dose has been attributed to carrier-mediated absorption (Stewart, et al., *Pharmaceutical Research* 10(2):276-281 (1993)).

20 In early work with rats, Vollmer, et al., *Arzneim-Forsch/Drug Research* 36(I, Nr. 5):781-892 (1986) found that the absorption site for gabapentin was the duodenum. The absorption of gabapentin occurs relatively slowly with the peak plasma concentration occurring approximately 2-6 hours after dosing (Bourgeois, *supra*). The elimination of gabapentin is exclusively through renal pathways (Chadwick, *The Lancet* 343:89-91 (1994); Vollmer, *supra*; Thomson, et al., *Clin. Pharmacokinet.* 23(3):216-230 (1992); and Riva, et al., *Clin. Pharmacokinet.* 31(6):470-493 (1996)) with reported half-lives of 5-7 hours (Chadwick, *supra*) and 6-7 hours (Gram, *supra*).

30 A once- or twice-daily dosage form of gabapentin would be expected to improve compliance and therefore a controlled release dosage form has some distinct advantages over the conventional immediate release formulations. In addition, a controlled release dosage form would lower the maximum plasma concentration, and this may result in reduced side effects. Since gabapentin is absorbed high in the gastrointestinal tract, by

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means of a saturable transport mechanism, a gastric retained dosage form is particularly beneficial for delivery of gabapentin since the dosage form would be able to keep the drug in the region of absorption and show improved bioavailability by virtue of the slower release rate that avoids saturation of the carrier mediated transport of conventional dosages.

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Summary Of The Invention

One aspect of the invention relates to a method of treating epilepsy comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

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Yet another aspect of the invention relates to a method of treating neuropathic pain comprising administering a therapeutically effective amount of gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form to a mammal in need of such treatment.

15

Still another aspect of the invention relates to an improved method of administering a therapeutically effective amount of gabapentin to a patient in need thereof, the improvement comprising administering gabapentin or a pharmaceutically acceptable salt thereof, in a gastric retained dosage form.

20

Description Of The Invention

The invention relates to a method of treating a disease state, such as epilepsy, by administering gabapentin in a once- or twice-daily gastric retained dosage form. The gastric retained dosage form is particularly beneficial for delivery of gabapentin due to its prolonged transit in the upper gastrointestinal tract, which allows the drug to be absorbed adequately in the preferred region of absorption. In addition, a gastric retained dosage form increases the t_{max} and allows for a smoother, more prolonged anti-spasmodic effect. This dosage form also lowers the C_{max} and may result in reduced incidence and/or severity of CNS side effects of the drug, such as somnolence, ataxia, fatigue and dizziness.

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Method of Treatment

The instant invention is a method of treating a disease state comprising administering a therapeutically effective amount of gabapentin, or a pharmaceutically

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where: Active = gabapentin
PEO Coagulant = poly(ethylene oxide), grade PolyOx Coagulant, NF FP
grade, manufactured by Union Carbide/Dow Chemical
Company
5 Methocel K15M = hydroxypropylmethylcellulose, grade Methocel K15M,
premium, manufacture by Dow Chemical Company
M.St. = magnesium stearate, NF, supplied by Spectrum Chemical
Company

The dissolution was determined in USP apparatus I (40 mesh baskets), 100 rpm, in
10 deionized water. Samples, 5 ml at each time-point, were taken without media replacement
at 1, 2, 4 and 8 hours.

The resulting cumulative dissolution profile, based upon a theoretical percent active
added to the formulations is presented in tabulated form below:

Time (hours)	Theoretical wt% of Active Released
	Sample A
1	20.6
2	32.4
4	49.7
6	63.1
8	74.0
10	82.6

15

Example 3

Three Gastric Retentive (GRTM) gabapentin formulas were manufactured utilizing a
standard granulation technique. The formulations manufactured are shown in tabulated
form below:

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Formulation for Clinical Trial Manufacture		
<i>Gabapentin GR8, 300-mg</i> (GR8, 300-mg)	<i>Gabapentin GR6, 300-mg</i> (GR6, 300-mg)	<i>Gabapentin GR8, 600-mg</i> (GR8, 600-mg)
44.76% Gabapentin	44.76% Gabapentin	61.11% Gabapentin
21.99% Methocel® K15M, premium	16.46% Methocel® K4M, premium	7.59% Methocel® K15M, premium
21.99% Sentry® PolyOx® WSR Coagulant, NF FP	21.99% Sentry® PolyOx® WSR 303, NF FP	27.09% Sentry® PolyOx® WSR 303, NF FP
7.49% Avicel® PH-101, NF	12.98% Avicel® PH-101, NF	0.00% Avicel® PH-101, NF
2.75% Methocel® E5, prem.	2.75% Methocel® E5, prem.	3.22% Methocel® E5, prem.
1.00% Magnesium Stearate, NF	1.00% Magnesium Stearate, NF	1.00% Magnesium Stearate, NF
670-mg (Tablet weight)	670-mg (Tablet weight)	982-mg (Tablet weight)
0.3937" X 0.6299"	0.3937" X 0.6299"	0.4062" X 0.75"
Mod Oval	Mod Oval	Mod Cap

Gabapentin was obtained from Plantex U.S.A. (Englewood Cliffs, NJ). Methocel® brand hydroxypropyl methylcellulose (also known as hypromellose), and Sentry® PolyOx® brand polyethylene oxide were obtained from Dow Chemical (Midland, Michigan). Methocel E5, premium is a USP type 2910 hydroxypropyl methylcellulose with number average molecular weight of on the order of 6000-8000 and a viscosity of 5 cps as a 2% aqueous solution at 20 °C. Methocel® K4M and Methocel® K15M are USP type 2208 hydroxypropyl methylcellulose with viscosities of 4000 cps and 15,000 cps, respectively, as a 2% aqueous solution at 20 °C, and number average molecular weights on the order of 80,000 and 100,000, respectively. Sentry® PolyOx® WSR 301, NF FP, Sentry® PolyOx® WSR Coagulant, NF FP and Sentry® PolyOx® WSR 303, NF FP have viscosity-average molecular weights of approximately 4,000,000, 5,000,000 and 7,000,000, respectively. Avicel PH-101, NF is microcrystalline cellulose supplied by FMC Corporation

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(54) Title: PHARMACEUTICAL FORMULATIONS AND SYSTEMS FOR IMPROVED ABSORPTION AND MULTISTAGE RELEASE OF ACTIVE AGENTS

(57) Abstract: The present invention pertains to pharmaceutical formulations and systems for delivery of active agents, wherein a first fraction of an active agent is suspended in a vehicle and a second fraction of active agent is solubilized in the vehicle, with the suspended fraction representing about 5 wt. % to about 80 wt. % of the active agent and the second fraction representing about 20 wt. % to about 95 wt. % of the active agent. One or more additional active agents, which may be fully solubilized, partially solubilized, or suspended, may also be present. The first and second fractions of the active agent may or may not have different release profiles. Generally, a significant fraction of the solubilized drug will release rapidly, providing for rapid onset, while the suspended drug may be formulated for delayed and/or sustained release.

WO 03/068186 A1

32
132
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**PHARMACEUTICAL FORMULATIONS AND SYSTEMS FOR IMPROVED
ABSORPTION AND MULTISTAGE RELEASE OF ACTIVE AGENTS**

TECHNICAL FIELD

5 The present invention relates generally to the field of drug delivery. More specifically, the invention relates to novel pharmaceutical compositions for administration of active agents to patients, wherein the compositions provide for multi-stage drug release. The invention additionally relates to processes for preparing the suspensions and methods of using the suspensions to administer an active agent to a patient. The invention has
10 utility in the fields of pharmaceutical formulation, pharmacology, and medicine.

BACKGROUND ART

 Those working in the fields of pharmaceutical formulation and drug delivery continue to be limited by a number of difficulties presented by different active agents. It
15 has proved particularly problematic to provide therapeutically effective formulations for administration of drugs exhibiting low bioavailability and absorption. A well-designed formulation must, at a minimum, be capable of presenting a therapeutically effective amount of the active agent to the desired absorption site, in an absorbable form. Even this minimal functionality can be difficult to achieve, however, e.g., when delivery of a hydrophobic
20 active agent requires interaction with aqueous physiological environments, such as gastric fluids and intestinal fluids.

 A number of approaches to formulating active agents having low aqueous solubility are known. One well-known approach uses surfactant micelles to solubilize and transport the therapeutic agent. Micelles are agglomerates of colloidal dimensions formed by
25 amphiphilic compounds under certain conditions. Micelles, and pharmaceutical compositions containing micelles, have been extensively studied and are described in detail in the literature; see, e.g., *Remington: The Science and Practice of Pharmacy, Nineteenth Ed.* (Easton, PA: Mack Publishing Company, 1995). In aqueous solution, micelles can incorporate hydrophobic therapeutic agents in the hydrocarbon core of the micelle, or
30 entangled at various positions within the micelle walls. Although micellar formulations can solubilize a variety of hydrophobic therapeutic agents, the loading capacity of conventional

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anti-fungal agents, such as amphotericin, butenafine, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, oxiconazole, terbinafine, terconazole, tioconazole and undecenoic acid;

5 anti-gout agents, such as allopurinol, probenecid and sulphin-pyrazone;

antihistamines and allergy medications, such as acrivastine, astemizole, chlorpheniramine, cinnarizine, cetirizine, clemastine, cyclizine, cyproheptadine, desloratadine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, epinastine, fexofenadine, flunarizine, loratadine, meclizine, mizolastine, oxatomide, and terfenadine;

10 anti-malarials, such as amodiaquine, chloroquine, chlorproguanil, halofantrine, mefloquine, proguanil, pyrimethamine and quinine sulfate;

agents for treating headaches, including anti-migraine agents, such as almotriptan, butorphanol, dihydroergotamine, dihydroergotamine mesylate, eletriptan, ergotamine, frovatriptan, methysergide, naratriptan, pizotiline, rizatriptan, sumatriptan, tonabersat, and

15 zolmitriptan;

anti-muscarinic agents, such as atropine, benzhexol, biperiden, ethopropazine, hyoscyamine, mepenzolate bromide, oxyphencyclimine, scopolamine, and tropicamide;

anti-protozoal agents, such as atovaquone, benznidazole, elioquinol, decoquinat, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furazolidone, metronidazole,

20 nimorazole, nitrofurazone, ornidazole and tinidazole;

anti-thyroid agents, such as carbimazole, paricalcitol, and propylthiouracil;

anti-tussives, such as benzonatate;

anxiolytics, sedatives, and hypnotics, such as alprazolam, amylorbarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal,

25 chlordiazepoxide, chlormethiazole, chlorpromazine, chlorprothixene, clonazepam, clobazam, clotiazepam, clozapine, dexamethylphenidate (d-threo-methylphenidate) diazepam, droperidol, ethinamate, flunamisone, flunitrazepam, trifluorpromazine, flupenthixol decanoate, fluphenazine, flurazepam, gabapentin, gaboxadol, γ -hydroxybutyrate, haloperidol, lamotrigine, lorazepam, lormetazepam, medazepam, meprobamate, mesoridazine,

30 methaqualone, methylphenidate, midazolam, modafinil, molindone, nitrazepam, olanzapine, oxazepam, pentobarbitone, perphenazine pimozide, pregabalin, prochlorperazine,

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selection of the binder should be made on the basis of the type of equipment that is used. The size and size distribution of pellets, bulk density, strength, and flow properties also affect the performance of the pellets, and these properties can be adjusted by one skilled in the art by the inclusion of additives, choice of equipment, and processing conditions.

- 5 **Extrusion:** Extrusion is a well-known method of applying pressure to a damp or melted composition until it flows through an orifice or a defined opening. The extrudable length varies with the physical characteristics of the material to be extruded, the method of extrusion, and the process of manipulation of the particles after extrusion. Various types of extrusion devices can be employed, such as screw, sieve and basket, roll, and ram
- 10 extruders.

Encapsulation by Extrusion: In this method, the particles' components are added to a low moisture melt of a saccharide, e.g., a low maltodextrin (or sucrose or modified edible starch), mixed and extruded into a cold bath. The solidified composition can be further ground down. Optionally, centrifugal extrusion can be utilized for efficiency.

- 15 **Melt Extrusion:** The active agent particles can also be melted and extruded with a continuous, solvent-free extrusion process, with or without inclusion of additives.

- Spheronization:** Spheronization, as the term suggests, is the process of converting material into spheres, the particle shape having the lowest ratio of surface area to volume. Spheronization typically begins with damp extruded particles. The extruded particles are
- 20 broken into uniform lengths and gradually transformed into spherical shapes. In addition, powdered raw materials, which require addition of either liquid or material from a mixer, can be processed in an air-assisted spheronizer.

- Disk Spinning:** Spinning disk technology involves formation of particles from either a molten or solubilized composition sprayed onto a rotating disc maintained at a
- 25 predetermined temperature and rotating at a predetermined speed. When a molten composition contacts the spinning disk, particles congeal, while with a liquid composition, the liquid rapidly evaporates from the solution resulting in formation of solid drug particles. The composition may or may not contain various inert excipients and additives in addition to the active agent or agents. As will be appreciated by those of ordinary skill
- 30 in the art, the temperature of the disc and its rotation may be adjusted to produce particles of predetermined size and shape.

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Wurster process, an air suspension technique, is more suitable for encapsulations involving very fine powders.

Solvent-Free Coating: This process entails using coating materials that can be applied in a molten state. The selection of proper coating materials depends on melting point, melting point range, and the viscosity in the liquid state. A fluidized bed is ideal for molten coatings of substrates that range from about 100 micrometers to about 2000 micrometers in size. Fluidized bed coating using sprayed molten materials involves achieving a proper balance of process parameters that allow proper encapsulation to occur. Substrate particles that are suspended and separated from each other by the fluidization air enter a zone of finely atomized coating liquid. Coating occurs as the liquid droplets, which are substantially smaller in size than the substrate, impact the particles, spread, and solidify. Multiple layers can be coated, and the completion of spraying is followed by a product stabilization or cooling step. Some critical success parameters include bed temperature, atomization, atomization fluid temperature, droplet size, spray type, spray rate, rate of coating droplet solidification on particle surfaces, particle size, shape, etc. Inert materials such as sodium chloride, citric acid, and potassium chloride can serve as substrates. One skilled in the art can readily adjust such parameters to achieve a satisfactory product.

The processes described above are suitable for producing substrate-based particles or non-substrate-based particles. In the latter case, the particulate material does not include any seed particle (e.g., a conventional drug or other additive aggregate starch or sugar bead). Instead, the compositions are processed, and the components are chosen, such that a solid composition is formed without need for a substrate bead. The particles formed can be in the form of beadlets, beads, granules, pellets, etc., that have an approximately homogenous distribution. These particulates can be produced by means of balling in pelletizers or fluid bed granulators, and compaction or extrusion/spheronization. In addition, these particulates can be produced using solvent-free spray congealing processes or dropping (globulization) methods. Dropping procedures involve conversion of aqueous solutions or suspensions to a solid form. Congealing of the liquid droplets in cooling baths can be aided by a chemical reaction (e.g., insoluble salt or

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complex formation), a sol/gel transition, or by freezing in a coolant bath of liquid nitrogen or halogenated hydrocarbons.

VI. STABILIZING AGENTS:

5 The formulations of the present invention optionally include one or more stabilizing agents to increase the stability and/or compatibility of the suspension when formulated into a dosage form. Suitable stabilizing agents are suspending agents, flocculating agents, thickening agents, gelling agents, buffering agents, antioxidants, preservatives, antimicrobial agents, and mixtures thereof. Ideally, the agent acts to
10 minimize irreversible aggregation of suspended particles, and to maintain proper flow characteristics to ease manufacturing processes, e.g., to ensure that the formulation can be readily pumped and filled into desired dosage forms, such as capsules. In some instances, however, it may be desirable that the formulation have a high viscosity, so that no leakage will occur before a capsule or other dosage form is permanently sealed.

15 A preferred stabilizing agent in most cases is a suspending agent that imparts increased viscosity and retards sedimentation, to prevent caking. Any pharmaceutically acceptable excipient with such attributes, of the many well known in the art, can be used as such a suspending agent. Suitable suspending agents include cellulose derivatives, clays, natural gums, synthetic gums, or other agents known in the art. Specific suspending
20 agents, by way of example, include microcrystalline cellulose, sodium carboxymethylcellulose, powdered cellulose, ethymethylcellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, ethylhydroxy ethylcellulose, hydroxypropyl cellulose, attapulgit, bentonite, hectorite, montmorillonite, silica gel, fumed silicon dioxide, colloidal silicon dioxide, acacia, agar, carrageenan, guar gum,
25 locust bean gum, pectin, sodium alginate, propylene glycol alginate, tamarind gum, xanthan gum, carbomer, povidone, sodium starch glycolate, starches, tragacanth, magnesium aluminum silicate, aluminum silicate, magnesium silicate, gelatin, and glycyrrhizin. These suspending agents can further impart different flow properties to the suspension. The flow properties of the suspension can be Newtonian, plastic,
30 pseudoplastic, thixotropic or combinations thereof. Mixtures of suspending agents may also be used to optimize flow properties and viscosity.

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on a dosage form, e.g., on a capsule, tablet, or caplet, or on each of a plurality of granules, beads, or pellets. The bile salt or acid may take any number of physical forms, e.g., it may be in crystalline, amorphous, nanosized, micronized or milled form.

5 **VIII. DOSAGE FORMS AND ADMINISTRATION ROUTES:**

The pharmaceutical compositions and systems of the present invention are preferably formulated for oral administration, although other modes of administration are contemplated as well. For oral administration, the suspension can be formulated as a liquid or solid (e.g., powdered) concentrate, or as an aqueous or organic diluted
10 concentrate. In the diluted form, the diluent can be water, an aqueous solution, a buffer, an organic solvent, a beverage, a juice, or mixtures thereof. If desired, the diluent can include components dissolved or suspended therein, such as an active agent, an enzyme inhibitor, solubilizers, additives, and the like.

In a preferred embodiment, the oral dosage form is comprised of an encapsulated
15 composition, wherein the pharmaceutical formulation is typically contained in a capsule. The capsule can be a hard or soft gelatin capsule, a starch capsule, or a cellulosic capsule. For a two-piece capsule, the capsule can be further sealed either by a banding or a spray sealing mechanism after filling with the suspension formulation. Such dosage forms (as well as other solid dosage forms, such as tablets, caplets, granules, pellets, and beads) can
20 further be coated with, for example, a seal coating, an enteric coating, an extended release coating, a targeted delayed release coating, a film coating, a barrier coating, a compressed coating, a fast disintegrating coating, or an enzyme degradable coating. As a result, the dosage form can be designed for immediate release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release.

25 Multicompartment capsules can also be utilized for multi-stage release or pulsatile release of one or more than one active agent. Different active agents can be mixed or separated in different compartments such that they can be released at different stages or released according to different profiles. Multiple coatings can be applied for a desired performance.

30 The formulations of the invention can also be formulated as an osmosis-based dosage form for oral administration or for implants. The osmosis-based dosage form can

CLAIMS

1. A pharmaceutical formulation, comprising:
- (a) an active agent having a first fraction and a second fraction, wherein the first
- 5 fraction is comprised of a plurality of solid particles; and
- (b) a pharmaceutically acceptable vehicle comprising at least one compound selected from the group consisting of a hydrophilic surfactant, a lipophilic surfactant, a triglyceride and a solubilizer,
- wherein the first fraction of the active agent is suspended in the vehicle and the
- 10 second fraction of the active agent is solubilized in the vehicle, said first fraction representing about 5 wt.% to about 80 wt.% of the active agent and said second fraction representing about 20 wt.% to about 95 wt.% of the active agent.
2. The pharmaceutical formulation of claim 1, further including an additional active
- 15 agent.
3. The pharmaceutical formulation of claim 2, wherein the additional active agent is (a) suspended in the vehicle, (b) partially solubilized and partially suspended in the vehicle, or (c) fully solubilized in the vehicle.
- 20
4. The pharmaceutical formulation of claim 2, wherein the additional active agent is at least partially solubilized in the vehicle.
5. The pharmaceutical formulation of claim 1, wherein the first fraction represents
- 25 about 5 wt.% to about 80 wt.% of the active agent, and the second fraction represents about 20 wt.% to about 95 wt.% of the active agent.
6. The pharmaceutical formulation of claim 5, wherein the first fraction represents about 30 wt.% to about 80 wt.% of the active agent, and the second fraction represents
- 30 about 20 wt.% to about 70 wt.% of the active agent.

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7. The pharmaceutical formulation of claim 6, wherein the first fraction represents about 50 wt.% to about 70 wt.% of the active agent, and the second fraction represents about 30 wt.% to about 50 wt.% of the active agent.

5 8. The pharmaceutical formulation of claim 1, wherein the solid particles are comprised of powder, granules, pellets, beads, or combinations thereof.

9. The pharmaceutical formulation of claim 1, wherein the solid particles are associated with each other to form at least one dosage unit comprised of a granule, pellet,
10 bead or tablet suspended in the vehicle.

10. The pharmaceutical formulation of claim 1, wherein the solid particles are contained within at least one capsule suspended in the vehicle.

15 11. The pharmaceutical formulation of claim 1, wherein the solid particles are prepared by a process selected from melt extrusion, nanoencapsulation, lyophilization, spheronization, coacervation, cryopelletization, crystallization, antisolvent precipitation, precipitation from expanded supercritical fluid, spray drying, spray coating, spray
congealing, and combinations thereof.

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12. The pharmaceutical formulation of claim 11, wherein the solid particles are subjected to further processing after preparation thereof.

13. The pharmaceutical formulation of claim 12, wherein the further processing
25 comprises size reduction.

14. The pharmaceutical formulation of claim 13, wherein the size reduction is carried out by a process selected from grinding, milling, micronization, nanosizing, and combination thereof.

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15. The pharmaceutical formulation of claim 14, wherein the solid particles have a mean diameter in the range of about 0.1 μm to about 100 μm .

16. The pharmaceutical formulation of claim 13, wherein the size reduction is
5 carried out in the presence of a surfactant, a hydrophilic polymer, a lipid, a gelatin, a saccharide, or a mixture thereof.

17. The pharmaceutical formulation of claim 13, wherein the size reduction is carried out in the presence of the vehicle.

10

18. The pharmaceutical formulation of claim 12, wherein the further processing comprises treatment with an interfacial modifying agent selected from the group consisting of surfactants, hydrophilic polymers, lipids, gelatins, saccharides, and mixtures thereof.

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19. The pharmaceutical formulation of claim 18, wherein the treatment comprises coating the particles with the interfacial modifying agent.

20. The pharmaceutical formulation of claim 18, wherein the treatment comprises admixture of the particles with the interfacial modifying agent.

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21. The pharmaceutical formulation of claim 18, wherein the treatment comprises application of a dry powder of the interfacial modifying agent to the particles.

22. The pharmaceutical formulation of claim 18, wherein the treatment comprises
25 chemical interaction of the particles with the interfacial modifying agent.

23. The pharmaceutical formulation of claim 20, wherein the chemical interaction involves covalent attachment, ionic binding, hydrogen bonding, complexation, adsorption, or a combination thereof.

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24. The pharmaceutical formulation of claim 1, wherein the solid particles contain at least one pharmaceutically acceptable excipient.

25. The pharmaceutical formulation of claim 1, further comprising at least one
5 pharmaceutically acceptable additive selected from the group consisting of a stabilizing agent, an antioxidant, a bufferant, an antifoaming agent, a detackifier, a preservative, a chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an opacifier, a binder, a filler, a plasticizer, a taste-masking agent, a lubricant, and an enzyme inhibitor.

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26. The pharmaceutical formulation of claim 25, wherein said at least one pharmaceutically acceptable additive is a stabilizing agent.

27. The pharmaceutical formulation of claim 26, wherein the stabilizing agent is a
15 suspending agent.

28. The pharmaceutical formulation of claim 27, wherein the suspending agent is selected from the group consisting of microcrystalline cellulose, sodium carboxymethylcellulose, powdered cellulose, hydroxypropyl cellulose, hydroxypropyl
20 methylcellulose, methylcellulose, ethylcellulose, ethyl methylcellulose, ethyl hydroxyethylcellulose, attapulgate, bentonite, hectorite, montmorillonite, silica gel, fumed silicon dioxide, colloidal silicon dioxide, acacia, agar, carrageenan, guar gum, locust bean gum, pectin, sodium alginate, propylene glycol alginate, tamarind gum, xanthan gum, carbomers, polyvinyl pyrrolidone, starch, sodium starch glycolate, tragacanth, magnesium
25 aluminum silicate, aluminum silicate, magnesium silicate, gelatin, and glycyrrhizin.

29. The pharmaceutical formulation of claim 1, wherein the solid particles comprise at least one amorphous phase, at least one crystalline phase, or a mixture of at least one amorphous phase and at least one crystalline phase.

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30. The pharmaceutical formulation of claim 29, wherein the solid particles further include a stabilizing agent.

31. The pharmaceutical formulation of claim 30, wherein said stabilizing agent is
5 selected from the group consisting of synthetic hydrophilic polymers, surfactants, saccharides, gelatin, and combinations thereof.

32. The pharmaceutical formulation of claim 31, wherein the synthetic hydrophilic polymers are selected from the group consisting of polyalkylene oxides, polyalkylene
10 oxide-substituted C₂-C₆ diols and triols, polyalkylene oxide-substituted saccharides, poly(N-vinyl lactams), and polymers of carboxyvinyl monomers.

33. The pharmaceutical formulation of claim 32, wherein the synthetic hydrophilic polymers are selected from the group consisting of polyethylene glycol, mono-
15 poly(oxyethylene)-substituted propylene glycol, di-(polyoxyethylene)-substituted propylene glycol, mono-poly(oxyethylene)-substituted glycerol, di-(polyoxyethylene)-substituted glycerol, tri-(polyoxyethylene)-substituted glycerol, polyoxyethylated sorbitol, polyoxyethylated glucose, polyvinyl pyrrolidone, poly(N-vinyl caprolactam), and polymers and copolymers of acrylic acid, methacrylic acid and/or esters thereof.

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34. The pharmaceutical formulation of claim 31, wherein the saccharides are cellulosic polymers.

35. The pharmaceutical formulation of claim 34, wherein the stabilizing agent is
25 hydroxypropyl methylcellulose.

36. The pharmaceutical formulation of claim 1, wherein the vehicle is substantially free of water-indispersible wax materials.

30 37. The pharmaceutical formulation of claim 36, wherein the water-indispersible wax materials are selected from the group consisting of beeswax, paraffin, yellow wax,

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hydrogenated oils, hydrogenated vegetable oil, hydrogenated soybean oil flakes and mixtures thereof.

38. The pharmaceutical formulation of claim 1, wherein the vehicle is substantially
5 free of added water.

39. The pharmaceutical formulation of claim 1, wherein the vehicle contains less than about 20 wt.% water.

10 40. The pharmaceutical formulation of claim 1, wherein the vehicle contains less than about 10 wt.% water.

41. The pharmaceutical formulation of claim 1, wherein the vehicle comprises (a) at least one hydrophilic surfactant, (b) at least one lipophilic surfactant, or (c) at least one
15 hydrophilic surfactant and at least one lipophilic surfactant.

42. The pharmaceutical formulation of claim 41, wherein the vehicle comprises at least one hydrophilic surfactant and at least one lipophilic surfactant.

20 43. The pharmaceutical formulation of claim 1, wherein the vehicle comprises a triglyceride, a solubilizer, or a mixture thereof.

44. The pharmaceutical formulation of claim 1, wherein said at least one compound represents about 1 wt.% to about 99 wt.% of the formulation.

25 45. The pharmaceutical formulation of claim 44, wherein said at least one compound represents about 10 wt.% to about 90 wt.% of the formulation.

46. The pharmaceutical formulation of claim 45, wherein said at least one
30 compound represents about 20 wt.% to about 80 wt.% of the formulation.

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47. The pharmaceutical formulation of claim 1, wherein the active agent is selected from the group consisting of analgesic agents, anesthetic agents, anti-anginal agents, antiarthritic agents, anti-arrhythmic agents, antiasthmatic agents, antibacterial agents, anti-BPH agents, anticancer agents, anticholinergic agents, anticoagulants, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, anti-epileptic agents, antifungal agents, antigout agents, antihelminthic agents, antihistamines, antihypertensive agents, antiinflammatory agents, antimalarial agents, antimigraine agents, antimuscarinic agents, antinauseants, antineoplastic agents, anti-obesity agents, antiosteoporosis agents, antiparkinsonism agents, antiprotozoal agents, antipruritics, antipsychotic agents, antipyretics, antispasmodics, antithyroid agents, antitubercular agents, antilulcer agents, anti-urinary incontinence agents, antiviral agents, anxiolytics, appetite suppressants, attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) drugs, calcium channel blockers, cardiac inotropic agents, beta-blockers, central nervous system stimulants, cognition enhancers, corticosteroids, COX-2 inhibitors, decongestants, diuretics, gastrointestinal agents, genetic materials, histamine receptor antagonists, hormonolytics, hypnotics, hypoglycemic agents, immunosuppressants, keratolytics, leukotriene inhibitors, lipid-regulating agents, macrolides, mitotic inhibitors, muscle relaxants, narcotic antagonists, neuroleptic agents, nicotine, nutritional oils, parasympatholytic agents, sedatives, sex hormones, sympathomimetic agents, tranquilizers, vasodilators, vitamins, and combinations thereof.

48. The pharmaceutical formulation of claim 47, wherein the active agent is a lipid-regulating agent.

49. The pharmaceutical formulation of claim 48, wherein the lipid-regulating agent is selected from the group consisting of bezafibrate, beclobrate, binifibrate, ciplofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, ezetimibe, etofibrate, fenofibrate, fenofibric acid, gemfibrozil, nicosfibrate, pirifibrate, probucol, ronifibrate, simfibrate, and thecofibrate.

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50. The pharmaceutical formulation of claim 49, wherein the lipid-regulating agent is fenofibrate.

51. The pharmaceutical formulation of claim 47, wherein the active agent is a sex hormone.

52. The pharmaceutical formulation of claim 51, wherein the active agent is selected from the group consisting of progestins, estrogens, and combinations thereof.

53. The pharmaceutical formulation of claim 51, wherein the active agent comprises (a) a progestin selected from the group consisting of acetoxypregnenolone, allylestrenol, anagestone acetate, chlormadinone acetate, cyproterone, cyproterone acetate, desogestrel, dihydrogesterone, dimethisterone, ethisterone (17 α -ethynyltestosterone), ethynodiol diacetate, fluogestone acetate, gestadene, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxymethylprogesterone, hydroxymethylprogesterone acetate, 3-ketodesogestrel, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol, megestrol acetate, melengestrol acetate, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, normethisterone, and progesterone; and (b) an estrogen selected from the group consisting of 17 β -estradiol, 17 β -estradiol benzoate, 17 β -estradiol valerate, 17 β -estradiol cypionate, 17 β -estradiol heptanoate, 17 β -estradiol decanoate, 17 β -estradiol acetate, 17 β -estradiol diacetate, ethynylestradiol, ethynylestradiol 3-acetate, ethynylestradiol 3-benzoate, estriol, estriol succinate, polyestrol phosphate, estrone, estrone acetate, estrone sulfate, piperazine estrone sulfate, quinestrol, and mestranol.

54. The pharmaceutical formulation of claim 53, wherein the active agent comprises progesterone and 17 β -estradiol.

55. The pharmaceutical formulation of claim 52, wherein the active agent comprises an estrogen.

56. The pharmaceutical formulation of claim 55, wherein the estrogen is 17 β -estradiol.

5 57. The pharmaceutical formulation of claim 52, wherein the active agent comprises a progestin.

58. The pharmaceutical formulation of claim 57, wherein the progestin is progesterone.

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59. The pharmaceutical formulation of claim 1, wherein either the first fraction of the active agent, the second fraction of the active agent, or both the first and second fractions of the active agent are formulated for immediate release, pulsatile release, controlled release, extended release, delayed release, targeted release, or targeted delayed
15 release of the active agent.

60. The pharmaceutical formulation of claim 59, wherein the first fraction of the agent and the second fraction of the active agent have different release profiles.

20 61. The pharmaceutical formulation of claim 59, wherein the first fraction of the active agent further comprises a means for controlling release of the active agent from the suspended particles.

25 62. The pharmaceutical formulation of claim 61, wherein the second fraction of the active agent comprises an immediate release composition.

63. The pharmaceutical formulation of claim 61, wherein the second fraction of the active agent exhibits an immediate release profile.

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64. The pharmaceutical formulation of claim 63, wherein the second fraction provides for release of at least 50% of the active agent contained therein within 30 minutes at 37°C as evaluated using standard USP dissolution test equipment.

5 65. The pharmaceutical formulation of claim 64, wherein the second fraction provides for release of at least 75% of the active agent contained therein within 30 minutes at 37°C as evaluated using standard USP dissolution test equipment.

10 66. The pharmaceutical formulation of claim 65, wherein the second fraction provides for release of at least 90% of the active agent contained therein within 30 minutes at 37°C as evaluated using standard USP dissolution test equipment.

15 67. The pharmaceutical formulation of claim 1, further including a means for physically segregating the first and second fractions so as to prevent contact therebetween.

68. The pharmaceutical formulation of claim 67, wherein the means for physically segregating the first and second fractions is comprised of a vehicle-impermeable coating on the solid particles.

20 69. The pharmaceutical formulation of claim 67, wherein the solid particles of the second fraction are associated with each other to form at least one dosage unit comprised of a granule, pellet, bead or tablet, and the means for physically segregating the first and second fractions is comprised of a vehicle-impermeable coating on said at least one dosage unit.

25 70. The pharmaceutical formulation of claim 67, wherein the formulation is housed within a dosage form and the means for physically segregating the first and second fractions comprises a wall, a plug, a septum dividing the dosage form into a first region that contains the first fraction and a second region that contains the second fraction.

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71. The pharmaceutical formulation of claim 70, wherein the dosage form is a capsule.

72. A dosage form comprising the pharmaceutical formulation of claim 1.

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73. The dosage form of claim 71, comprised of a capsule, preconcentrate, drop, or drink.

74. A pharmaceutical system for administration of an active agent, comprising:

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(a) an active agent; and

(b) a pharmaceutically acceptable vehicle comprising at least one compound selected from the group consisting of a hydrophilic surfactant, a lipophilic surfactant, a triglyceride and a solubilizer,

15 wherein the relative amounts of the active agent and the vehicle are such that upon admixture thereof, a first fraction of the active agent is suspended in the vehicle, and a second fraction of the active agent is solubilized in the vehicle, wherein the second fraction represents about 20 wt.% to about 95 wt.% of the total active agent in the formulation.

20 75. The pharmaceutical system of claim 74, wherein the first fraction represents about 10 wt.% to about 80 wt.% of the active agent, and the second fraction represents about 20 wt.% to about 90 wt.% of the active agent.

25 76. The pharmaceutical system of claim 75, wherein the first fraction represents about 30 wt.% to about 80 wt.% of the active agent, and the second fraction represents about 20 wt.% to about 70 wt.% of the active agent.

77. The pharmaceutical system of claim 76, wherein the first fraction represents about 50 wt.% to about 70 wt.% of the active agent, and the second fraction represents about 30 wt.% to about 50 wt.% of the active agent.

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78. The pharmaceutical system of claim 77, wherein the solid particles are comprised of powder, granules, pellets, beads, or combinations thereof.

79. The pharmaceutical system of claim 74, wherein the solid particles are
5 associated with each other to form at least one dosage unit comprised of a granule, pellet, bead or tablet.

80. The pharmaceutical system of claim 79, wherein the solid particles are
10 contained within a capsule.

81. The pharmaceutical system of claim 79, wherein the solid particles are prepared
by a process selected from melt extrusion, nanoencapsulation, lyophilization,
spheronization, coacervation, cryopelletization, crystallization, antisolvent precipitation,
precipitation from expanded supercritical fluid, spray drying, spray coating, spray
15 congealing, and combinations thereof.

82. The pharmaceutical system of claim 81, wherein the solid particles are
subjected to further processing after preparation thereof.

20 83. The pharmaceutical system of claim 82, wherein the further processing
comprises size reduction.

84. The pharmaceutical system of claim 83, wherein the size reduction is carried
out by a process selected from grinding, milling, micronization, nanosizing, and
25 combination thereof.

85. The pharmaceutical system of claim 84, wherein the solid particles have a mean
diameter in the range of about 0.1 μm to about 100 μm .

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86. The pharmaceutical system of claim 83, wherein the size reduction is carried out in the presence of a surfactant, a hydrophilic polymer, a lipid, a gelatin, a saccharide, or a mixture thereof.

5 87. The pharmaceutical system of claim 83, wherein the size reduction is carried out in the presence of the vehicle.

88. The pharmaceutical system of claim 82, wherein the further processing comprises treatment with an interfacial modifying agent selected from the group consisting
10 of surfactants, hydrophilic polymers, lipids, gelatins, saccharides, and mixtures thereof.

89. The pharmaceutical system of claim 88, wherein the treatment comprises coating the particles with the interfacial modifying agent.

15 90. The pharmaceutical system of claim 88, wherein the treatment comprises admixture of the particles with the interfacial modifying agent.

91. The pharmaceutical system of claim 88, wherein the treatment comprises application of a dry powder of the interfacial modifying agent to the particles.

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92. The pharmaceutical system of claim 88, wherein the treatment comprises chemical interaction of the particles with the interfacial modifying agent.

93. The pharmaceutical system of claim 92, wherein the chemical interaction
25 involves covalent attachment, ionic binding, hydrogen bonding, complexation, adsorption, or a combination thereof.

94. The pharmaceutical system of claim 74, wherein the solid particles contain at least one pharmaceutically acceptable excipient.

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95. The pharmaceutical system of claim 74, wherein the vehicle further comprises at least one pharmaceutically acceptable additive selected from the group consisting of a stabilizing agent, an antioxidant, a bufferant, an antifoaming agent, a detackifier, a preservative, a chelating agent, a viscomodulator, a tonicifier, a flavorant, a colorant, an odorant, an opacifier, a binder, a filler, a plasticizer, a taste-masking agent, a lubricant, and an enzyme inhibitor.

96. The pharmaceutical system of claim 95, wherein said at least one pharmaceutically acceptable additive is a stabilizing agent.

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97. The pharmaceutical system of claim 96, wherein the stabilizing agent is a suspending agent.

98. The pharmaceutical system of claim 97, wherein the suspending agent is selected from the group consisting of microcrystalline cellulose, sodium carboxymethylcellulose, powdered cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, ethyl methylcellulose ethyl hydroxyethylcellulose, attapulgate, bentonite, hectorite, montmorillonite, silica gel, fumed silicon dioxide, colloidal silicon dioxide, acacia, agar, carrageenan, guar gum, locust bean gum, pectin, sodium alginate, propylene glycol alginate, tamarind gum, xanthan gum, carbomers, polyvinyl pyrrolidone, starch, sodium starch glycolate, tragacanth, magnesium aluminum silicate, aluminum silicate, magnesium silicate, gelatin, and glycyrrhizin.

99. The pharmaceutical system of claim 74, wherein the solid particles comprise at least one amorphous phase, at least one crystalline phase, or a mixture of at least one amorphous phase and at least one crystalline phase.

100. The pharmaceutical system of claim 99, wherein the solid particles further include a stabilizing agent.

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101. The pharmaceutical system of claim 100, wherein said stabilizing agent is selected from the group consisting of synthetic hydrophilic polymers, surfactants, saccharides, gelatin, and combinations thereof.

5 102. The pharmaceutical system of claim 101, wherein the synthetic hydrophilic polymers are selected from the group consisting of polyalkylene oxides, polyalkylene oxide-substituted C₂-C₆ diols and triols, polyalkylene oxide-substituted saccharides, poly(N-vinyl lactams), and polymers of carboxyvinyl monomers.

10 103. The pharmaceutical system of claim 102, wherein the synthetic hydrophilic polymers are selected from the group consisting of polyethylene glycol, mono-poly(oxyethylene)-substituted propylene glycol, di-(polyoxyethylene)-substituted propylene glycol, mono-poly(oxyethylene)-substituted glycerol, di-(polyoxyethylene)-substituted glycerol, tri-(polyoxyethylene)-substituted glycerol, polyoxyethylated sorbitol,
15 polyoxyethylated glucose, polyvinyl pyrrolidone, poly(N-vinyl caprolactam), and polymers and copolymers of acrylic acid, methacrylic acid and/or esters thereof.

104. The pharmaceutical system of claim 103, wherein the saccharides are cellulosic polymers.

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105. The pharmaceutical system of claim 104, wherein the stabilizing agent is hydroxypropyl methylcellulose.

106. The pharmaceutical system of claim 74, wherein the vehicle is substantially
25 free of water-indispersible wax materials.

107. The pharmaceutical system of claim 106, wherein the water-indispersible wax materials are selected from the group consisting of beeswax, paraffin, yellow wax, hydrogenated oils, hydrogenated vegetable oil, hydrogenated soybean oil flakes and
30 mixtures thereof.

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108. The pharmaceutical system of claim 74, wherein the vehicle is substantially free of added water.

109. The pharmaceutical system of claim 108, wherein the vehicle contains less
5 than about 20 wt.% water.

110. The pharmaceutical system of claim 109, wherein the vehicle contains less than about 10 wt.% water.

10 111. The pharmaceutical system of claim 110, wherein the vehicle comprises (a) at least one hydrophilic surfactant, (b) at least one lipophilic surfactant, or (c) at least one hydrophilic surfactant and at least one lipophilic surfactant.

112. The pharmaceutical system of claim 111, wherein the vehicle comprises at
15 least one hydrophilic surfactant and at least one lipophilic surfactant.

113. The pharmaceutical system of claim 74, wherein the vehicle comprises a triglyceride, a solubilizer, or a mixture thereof.

20 114. The pharmaceutical system of claim 74, wherein the active agent is selected from the group consisting of analgesic agents, anesthetic agents, anti-anginal agents, antiarthritic agents, anti-arrhythmic agents, antiasthmatic agents, antibacterial agents, anti-BPH agents, anticancer agents, anticholinergic agents, anticoagulants, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, anti-epileptic agents, antifungal agents,
25 antigout agents, antihelminthic agents, antihistamines, antihypertensive agents, antiinflammatory agents, antimalarial agents, antimigraine agents, antimuscarinic agents, antinauseants, antineoplastic agents, anti-obesity agents, antiosteoporosis agents, antiparkinsonism agents, antiprotozoal agents, antipruritics, antipsychotic agents, antipyretics, antispasmodics, antithyroid agents, antitubercular agents, antiulcer agents,
30 anti-urinary incontinence agents, antiviral agents, anxiolytics, appetite suppressants, attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD) drugs,

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calcium channel blockers, cardiac inotropic agents, beta-blockers, central nervous system stimulants, cognition enhancers, corticosteroids, COX-2 inhibitors, decongestants, diuretics, gastrointestinal agents, genetic materials, histamine receptor antagonists, hormonolytics, hypnotics, hypoglycemic agents, immunosuppressants, keratolytics, leukotriene inhibitors, lipid-regulating agents, macrolides, mitotic inhibitors, muscle
5 relaxants, narcotic antagonists, neuroleptic agents, nicotine, nutritional oils, parasympatholytic agents, sedatives, sex hormones, sympathomimetic agents, tranquilizers, vasodilators, vitamins, and combinations thereof.

10 115. The pharmaceutical system of claim 114, wherein the active agent is a lipid-regulating agent.

116. The pharmaceutical system of claim 115, wherein the lipid-regulating agent is selected from the group consisting of bezafibrate, beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, clofibric acid, etofibrate, ezetimibe, etofibrate, fenofibrate,
15 fenofibric acid, gemfibrozil, nicofibrate, pirifibrate, probucol, ronifibrate, simfibrate, and theofibrate.

117. The pharmaceutical system of claim 116, wherein the lipid-regulating agent is
20 fenofibrate.

118. The pharmaceutical system of claim 114, wherein the active agent is a sex hormone.

25 119. The pharmaceutical system of claim 118, wherein the active agent is selected from the group consisting of progestins, estrogens, and combinations thereof.

120. The pharmaceutical system of claim 118, wherein the active agent comprises
(a) a progestin selected from the group consisting of acetoxypregnenolone, allylestrenol, anagestone acetate, chlormadinone acetate, cyproterone, cyproterone acetate, desogestrel,
30 dihydrogesterone, dimethisterone, ethisterone (17 α -ethynyltestosterone), ethynodiol

diacetate, flurogestone acetate, gestadene, hydroxyprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxymethylprogesterone, hydroxymethylprogesterone acetate, 3-ketodesogestrel, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, megestrol, megestrol acetate, melengestrol acetate, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, 5 norethynodrel, norgestimate, norgestrel, norgestrienone, normethisterone, and progesterone; and (b) an estrogen selected from the group consisting of 17 β -estradiol, 17 β -estradiol benzoate, 17 β -estradiol valerate, 17 β -estradiol cypionate, 17 β -estradiol heptanoate, 17 β -estradiol decanoate, 17 β -estradiol acetate, 17 β -estradiol diacetate, ethynylestradiol, 10 ethynylestradiol 3-acetate, ethynylestradiol 3-benzoate, estriol, estriol succinate, polyestrol phosphate, estrone, estrone acetate, estrone sulfate, piperazine estrone sulfate, quinestrol, and mestranol.

121. The pharmaceutical system of claim 120, wherein the active agent comprises 15 progesterone and 17 β -estradiol.

122. The pharmaceutical system of claim 119, wherein the active agent comprises an estrogen.

20 123. The pharmaceutical system of claim 122, wherein the estrogen is 17 β -estradiol.

124. The pharmaceutical system of claim 118, wherein the active agent comprises a progestin.

25 125. The pharmaceutical system of claim 124, wherein the progestin is progesterone.

126. The pharmaceutical system of claim 74, wherein either the first fraction of the 30 active agent, the second fraction of the active agent, or both the first and second fractions of the active agent are formulated for immediate release, pulsatile release, controlled release,

extended release, delayed release, targeted release, or targeted delayed release of the active agent.

127. The pharmaceutical system of claim 126, wherein the first fraction of the
5 agent and the second fraction of the active agent have different release profiles.

128. The pharmaceutical system of claim 126, wherein the first fraction of the
active agent further comprises a means for controlling release of the active agent from the
suspended particles.

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129. The pharmaceutical system of claim 128, wherein the second fraction of the
active agent comprises an immediate release composition.

130. The pharmaceutical system of claim 128, wherein the second fraction of the
15 active agent exhibits an immediate release profile.

131. The pharmaceutical system of claim 130, wherein the second fraction provides
for release of at least 50% of the active agent contained therein within 30 minutes at 37°C
as evaluated using standard USP dissolution test equipment.

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132. The pharmaceutical system of claim 131, wherein the second fraction provides
for release of at least 75% of the active agent contained therein within 30 minutes at 37°C
as evaluated using standard USP dissolution test equipment.

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133. The pharmaceutical system of claim 132, wherein the second fraction provides
for release of at least 90% of the active agent contained therein within 30 minutes at 37°C
as evaluated using standard USP dissolution test equipment.

134. A method of administering an active agent to a mammalian patient, the method
30 comprising orally administering to the patient an amount of the formulation of claim 1
sufficient to deliver a therapeutically effective amount of the active agent to the patient.

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135. The method of claim 134, wherein the mammalian patient is human.

136. A method of administering an active agent to a mammalian patient, the
5 method comprising orally administering to the patient a drug delivery system comprised of
(a) an active agent; and (b) a pharmaceutically acceptable vehicle comprising at least one
compound selected from the group consisting of a hydrophilic surfactant, a lipophilic
surfactant, a triglyceride and a solubilizer, wherein the relative amounts of the active agent
and the vehicle are such that upon admixture thereof, a first fraction of the active agent is
10 suspended in the vehicle, and a second fraction of the active agent is solubilized in the
vehicle, wherein the second fraction represents about 20 wt.% to about 95 wt.% of the total
active agent in the formulation.

137. The method of claim 136, wherein the active agent, the vehicle and the at least
15 one compound are administered simultaneously.

138. The method of claim 137, wherein the active agent, the vehicle and the at least
one compound are administered in a single formulation.

20 139. The method of claim 136, wherein at least two of the active agent, the vehicle
and the at least one compound are not administered simultaneously.

140. The method of claim 139, wherein said at least two of the active agent, the
vehicle and the at least one compound are housed in different dosage forms.

25 141. In a method for reducing interpatient variability with respect to absorption and
bioavailability of an orally administered pharmaceutical formulation containing an active
agent, the improvement comprising administering the active agent in the pharmaceutical
formulation of claim 1.

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142. A method for reducing the effect of food on absorption and bioavailability of an active agent orally administered to a patient, comprising administering the active agent to the patient in the pharmaceutical formulation of claim 1.

- 5 143. A method for increasing the onset of a therapeutic effect associated with administration of an active agent to a patient, comprising administering the active agent to the patient in the pharmaceutical formulation of claim 1.

- 10 144. A method for both increasing the onset of a therapeutic effect associated with administration of an active agent to a patient and reducing the time to apparent elimination, comprising administering the active agent to the patient in the pharmaceutical formulation of any one of claims 12, 13 or 18.

- 15 145. A method for both increasing the onset of a therapeutic effect associated with administration of an active agent to a patient and providing for an extended duration of drug release, the therapeutic effect, or both, comprising administering the active agent to the patient in the pharmaceutical formulation of claim 61.

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PCT

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(81) Designated States (*national*): AF, AG, AI, AM, AT, AU,
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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
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GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
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WO 03/002151 A1

(54) Title: **ORAL PHARMACEUTICAL COMPOSITIONS WITH MODIFIED RELEASE OF THE ACTIVE INGREDIENT**

(57) Abstract: The present invention relates to modified-release oral pharmaceutical compositions containing one or more active principles solubilised, suspended or embedded in a suitably formulated amphiphilic matrix which, loaded in hydrophilic matrices, provides different release profiles.

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161CLAIMS

1. Oral controlled-release pharmaceutical compositions, comprising:
 - a) a matrix consisting of amphiphilic compounds either liquid or with melting point below 60°C, possibly to form eutectic mixture melting at 35-37°C, in which the active ingredient is at least partially soluble and/or dispersed and/or inglobated or granulated with amphiphilic compound previously solubilised or suspended in solvent (preferably water);
 - b) a surface acting component which is compatible with the amphiphilic matrix and can be homogeneously solubilized and/or dispersed in the amphiphilic matrix;
 - c) a component based on cyclodextrins and/or polymers which can be dispersed in the surface-activated amphiphilic matrix or can in turn be loaded on the optionally surface-activated amphiphilic matrix, to obtain a liquid, semisolid or solid form;
 - d) a hydrophilic matrix in which the complex amphiphilic matrix is dispersed and part of the active ingredient can be dispersed;
 - e) any other excipients.
2. Compositions as claimed in claim 1 wherein the amphiphilic compounds comprise glycol alkyl ethers such as diethylene glycols monoethyl ether; macrogolglycerids such as mixtures of mono- and triglycerids and of mono- and diesters of polyethylene glycols and of fatty acids, polyethylene glycols hydroxystearates.
3. Composition as claimed in claims 1 and/or 2, wherein surfactants comprise phosphatides, phosphatidyl cholines, phosphatidyl diethanolamines, sphingomyelins, anionic and non-ionic emulsifying waxes, sodium lauryl sulfate, sodium dodecyl sulfate, polysorbates, cholic

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acids, poloxamer, sodium sulfosuccinate, sodium lauryl sarcosinate, dioctylsodium sulfosuccinate.

4. Composition as claimed in the above claims wherein cyclodextrins comprise alpha-beta-gamma cyclodextrins, hydroxyethylcyclodextrins, 5 methylecyclodextrins, hydroxypropylcyclodextrins.

5. Composition as claimed in the above claims, wherein polymers comprise sodium croscarmellose, cross-linked polyvinylpyrrolidone, amberlites.

6. Composition as claimed in the above claims, wherein the active 10 ingredient is in part present in the amphiphilic matrix and in part loaded on the cyclodextrins and/or polymers, in the form of minitablets, granules or microgranules.

7. Composition as claimed in the above claims, wherein the amphiphilic matrix is loaded on a hydrophilic matrix consisting of hydrogels.

8. Composition as claimed in the above claims, wherein hydrogels 15 comprise substances selected from acrylic or methacrylic polymers or copolymers, alkylvinyl polymers, celluloses, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, alginates, pectins, starches and derivatives, natural and synthetic gums, polycarbophil, chitosans.

9. Composition according to any one of the above claims comprising a 20 gastro-soluble or gastro-resistant coating of cellulose derivatives and/or methacrylic acid polymers.

10. Composition according to any one of the above claims, wherein the active ingredient belongs to therapeutical categories selected from 25 antineoplastics and immunomodulators, detoxicant compounds for cytostatic treatments, anti-inflammatories, analgesics and antirheumatics, drugs for the treatment of bone diseases, antitussives, systemic antihistamines, antiemetics, antinausea agents, antipropulsives, oral hypoglycemizing

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antidiabetics, cathartics, antihypertensives, ace-inhibitors, betablockers and coronarodilators, calcium antagonists, antiparkinson drugs, intestinal anti-inflammatories, anxiolytics, antiepileptics, alpha-blockers, diuretics, hypolipemizing agents, 5HT1 selective antagonists, anticholinergics, 5 lissives, antidepressants, antibiotics.

11. Compositions as claimed in claim 7, wherein the active ingredient is selected from etoposide, calcium folinate, methotrexate, cyclophosphamide, procarbazine, fluorouracil, idarubicin, gylpizide, glybenclamide, flutamide, nimesulide, piroxicam, ketoprofen, ibuprofen, gabapentin, 5-aminosalicylic, 10 budesonide, metformin, mesalamine.

12. A process for the preparation of the compositions of claims 1 to 9, which comprises the following steps:

- a) adding surfactants to the amphiphilic matrix, to obtain a homogeneous solution or dispersion;
- 15 b) solubilizing, suspending, dispersing, totally or partly embedding one or more active principles;
- c) adding cyclodextrins and/or polymers, or granulating or dispersing with cyclodextrins and/or polymers;
- d) adding a hydrophilic matrix;
- 20 e) optionally adding excipients;
- f) optionally film-coating with cellulose derivatives or methacrylic polymers.



(2.001), ante mí, JORGE ENRIQUE CAICEDO ZAMORANO, Notario
T E R C E R O (3o.) del Círculo de Cali, - - - - -

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

ESTE PAPEL NO TIENE COSTO ALGUNO PARA EL USUARIO

27 AGO-2008

REPUBLICA DE COLOMBIA
NOTARIO NOVENO
BOGOTÁ, D.C.

LUZ MERY CORREA C
ELABORACION DE ESCRITURAS
Notaría 3 de Cali

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

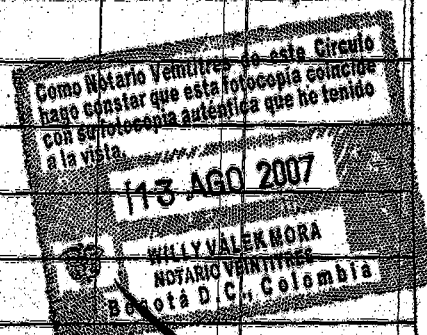
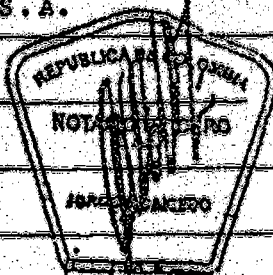
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

Se agregan comprobantes. Derechos \$30.000.00 Decreto 1681 de Septiembre 16 de 1996. Reformado mediante Resolución No.5839 de Diciembre 27 del año 2.000 y Decreto 1326 de Julio 06 del año 2.001. Se corrió en la hoja número AA 3286877. ENMENDADO "OCTUBRE" VALE.

9/ *Juan m. Barberi*

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO





165

CERTIFICADO NACIONAL
CAMARA DE COMERCIO DE CALI
 Fecha: 20080827 Hora: Certificado: 11:48:54
 Operación: 02CP20827018 PAGINA No. 1

CERTIFICADO DE REGISTRO

NOMBRE: TECNOQUIMICAS S.A.

SIGLA: TQ S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL: C.C. 287-39

DIRECCION NOTIFICACION JUDICIAL: C. 23-7-39

CUIDAD: CALI

MATRICULA MERCANTIL NRO.: 7049-4 **FECHA MATRICULA:** 01 DE JULIO DE 1957

AFFILIADO

QUE POR ESCRITURA NRO. 2670 DEL 12 DE JUNIO DE 1957, NOTARIA SEGUNDA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 01 DE JULIO DE 1957 BAJO EL NRO. 16627 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD DENOMINADA COMPANIAS TECNOQUIMICAS LIMITADA. CERTIFICA: QUE POR ESCRITURA NRO. 8438 DEL 30 DE DICIEMBRE DE 1970, NOTARIA SEGUNDA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 07 DE ENERO DE 1971 BAJO EL NRO. 42260 DEL LIBRO IX, LA SOCIEDAD SE TRANSFORMO DE SOCIEDAD LIMITADA EN SOCIEDAD EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC)



QUE POR ESCRITURA NRO. 2139 DEL 21 DE ABRIL DE 1972 NOTARIA SEGUNDA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 26 DE ABRIL DE 1972 BAJO EL NRO. 79 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE COMPANIAS TECNOQUIMICAS LIMITADA COMANDITA POR ACCIONES (SIC) POR EL DE TECNOQUIMICAS LIMITADA & CIA S.C. A. ...

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha: 20080827 Hora: Certificado 11:48:54

Operacion: 02CP20827018 PAGINA No. 2

CERTIFICA:

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

CERTIFICA:

QUE POR ESCRITURA NRO. 5664 DEL 12 DE DICIEMBRE DE 2005, NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 19 DE DICIEMBRE DE 2005 BAJO EL NRO. 14102 DEL LIBRO IX, SE APROBO LA FUSION POR ABSORCION ENTRE (ABSORBENTE) TECNOQUIMICAS S.A. Y (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 MAYO DE 2008, NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 16 DE MAYO 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 FECHA INS NRO.

INS LIBRO E.P. 4075 05/09/1957 NOTARIA SEGUNDA DE CALI 27/09/1957

16922 28/11/1957 NOTARIA SEGUNDA DE CALI 30/12/1957

5718 31/12/1957 NOTARIA PRIMERA DE CALI 13/03/1958

17242 16/07/1958 NOTARIA PRIMERA DE CALI 17/10/1958

5507 29/07/1958 NOTARIA PRIMERA DE CALI 17/10/1958

18365 17/12/1958 NOTARIA PRIMERA DE CALI 12/05/1959

3124 12/05/1959 NOTARIA PRIMERA DE CALI 03/06/1959

18366 20/06/1961 NOTARIA PRIMERA DE CALI 07/07/1961

5726 20/06/1961 NOTARIA PRIMERA DE CALI

19258

2374

19368

E.P. 2793

20/06/1961 NOTARIA PRIMERA DE CALI

07/07/1961

CONTINUA



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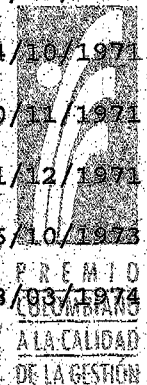


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CERTIFICADO NACIONAL
CAMARA DE COMERCIO DE CALI
Fecha: 20080827 Hora Certificado: 11:48:54
Operacion: 02CP20827018 PAGINA No 3

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23850	E.P.	3396	28/05/1963	NOTARIA PRIMERA DE CALI	11/06/1963
26016	E.P.	8853	30/12/1963	NOTARIA PRIMERA DE CALI	23/01/1964
27107	E.P.	5718	28/11/1957	NOTARIA SEGUNDA DE CALI	10/02/1964
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27682	E.P.	7057	21/10/1964	NOTARIA PRIMERA DE CALI	22/10/1964
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39341	E.P.	5211	27/08/1970	NOTARIA SEGUNDA DE CALI	04/09/1970
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44367	E.P.	8042	03/12/1971	NOTARIA SEGUNDA DE CALI	21/12/1971
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CONTINUA



CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

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Operacion: 02CP20827018 PAGINA No. 4

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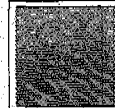
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

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Operacion : 02CP20827018

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 LIGITA 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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ALA CALIDAD
DE LA GESTION

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado : 11:48:54

Operacion : 02CP20827018 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) 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?DOS 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 POL?TICAS 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 CIEN MIL D?LARES AMERICANOS (\$US100.000.00). 4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD 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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188

CERTIFICADO NACIONAL
CAMARA DE COMERCIO DE CALI
Fecha : 20080827 Hora Certificado 11:48:54
Operacion : 02CP20827018 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 CUANTIA ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRICTAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA:
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IMPRESO POR DANARREDO S.A. INT. 0805111-8 0801 01 2008

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 de Comercio Hora Certificado: 11:48:54

Operation : 02CP20827018 PAGINA No. 8

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

ORIGEN: JUNTA DIRECTIVA

INSCRIPCION: 26 DE ENERO DE 1993 No. 62203 DEL LIBRO IX

FUE(IRON) NOMBRADO(S)

PRESIDENTE EJECUTIVO

FRANCISCO JOSE BARBERI OSPINA

C.C. 14445880

VICEPRESIDENTE EJECUTIVO

JUAN MANUEL BARBERI OSPINA

C.C. 14949561

VICEPRESIDENTE EJECUTIVO

JUAN BAUTISTA DE LOS RIOS GUTIERREZ

C.C. 17108621

VICEPRESIDENTE EJECUTIVO

EMILIO SARDI APARICIO

C.C. 14434582

CERTIFICA:

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

ORIGEN: ASAMBLEA DE ACCIONISTAS

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

FUE(IRON) NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

FRANCISCO JOSE BARBERI OSPINA

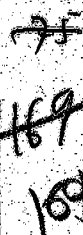
C.C. 14445880

SEGUNDO RENGLON

JUAN MANUEL BARBERI OSPINA

C.C. 14949561

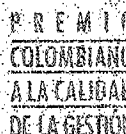
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DEL 31 DE MARZO DE 2003

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**P R E M I O
COLOMBIANO
A LA CALIDAD
DE LA GESTIÓN**

DOCUMENTO: ACTA No. 59

ICGTEC
 SEXTO
 MARTI
 C.C. 3
 CERTIFICADO
 DE GESTION
 DE CALIDAD
 Registrado No 8274
 DOCUMENTO
 CIG-254-0204-2004

2003-09-10 14:00

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha: 1-20080827 de com Hora: certificado 11:48:54

Operacion: 02CP20827018

PAGINA No 10

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 23 DE ABRIL DE 2003 No: 2845 DEL LIBRO IX
FUE (RON) NOMBRADO (S):

REVISOR FISCAL

DELOITTE & TOUCHE LTDA D & T LTDA

NIT: 8600058134

CERTIFICADO

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AGOSTO DE 2004

ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA

INSCRIPCION: 30 DE AGOSTO DE 2004 No: 3417 DEL LIBRO IX

FUE (RON) NOMBRADO (S)

REVISOR FISCAL PRINCIPAL

DE LOUIS FERNANDO QUICHENO BENAVIDES

C.C. 6106227

REVISOR FISCAL SUPLENTE

JESUS DARIO LOPEZ CASELLA

C.C. 16789097

QUE POR ESCRITURA NRO. 5235 DEL 19 DE JULIO DE 1996

INSCRITA EN LA CAMARA DE COMERCIO EL 25 DE JULIO DE 1996 BAJO EL NRO. 144 DEL

MEMBRERO POR MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL AMPLIO Y SUFICIENTE A

CARLOS ALBERTO QUINTERO MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO

CON LA Cedula de Ciudadania NRO. 1440 778 DE CALI

PERSONERIA OSTENTA EL REPRESENTANTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN

LA ADMINISTRACION DE IMPUESTOS Y ADUANAS NACIONALES O DEL ORGANISMO QUE HAGAN

SUS VECES Y FIRMAR EN REPRESENTACION DE LA SOCIEDAD LAS DECLARACIONES DEL

IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS QUE CORRESPONDA A LA SOCIEDAD

TODAS LAS DEMAS DECLARACIONES QUE LA SOCIEDAD DEBA PRESENTAR ANTE DICHA

ENTIDAD, TALES COMO LA DE VENTAS, RETENCION EN LA FUENTE Y TIMBRE Y CUALESQUIER

OTRA SINIESTRA DE COMERCIO DE BOGOTA CAMARA DE COMERCIO DE BOGOTA CAMARA DE COMERCIO

PARA PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827

Hora Certificado 11:48:54

Operacion : 02CP20827018

PAGINA No: 11

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 ENERO DE 2002 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 13 DE FEBRERO 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 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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado 11:48:54

Operacion : 02CP20827018 PAGINA No. 12

 CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTIA INDICADA. 6o. REPRESENTAR A TECNOQUIMICAS S.A. DENTRO DE LOS TRAMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACION ECONOMICA PREVISTO EN LA LEY 550 DE 1999 Y LAS NORMAS QUE LA ADICIONEN O MODIFIQUEN Y LIQUIDACIONES OBLIGATORIAS QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE ACREEDORES O ANTE LOS JUZGADOS CIVILES, CON EXPRESAS FACULTADES PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER, NOMBRAR APODERADOS, PRESENTAR LOS CREDITOS, APORTAR LAS PRUEBAS QUE ESTIME NECESARIAS, ASISTIR A LAS AUDIENCIAS PRELIMINARES Y DEFINITIVAS, ACORDAR FORMULAS DE PAGO, RECIBIR Y EN GENERAL PARA EJERCER TODAS AQUELLAS GESTIONES NECESARIAS PARA OBTENER EL RECONOCIMIENTO Y PAGO DE LOS CREDITOS PRESENTADOS. LAS FACULTADES AQUI ESTABLECIDAS ESTAN LIMITADAS PARA LOS CREDITOS HASTA POR CUANTIA DE QUINIENTOS (500) SALARIOS MINIMOS LEGALES MENSUALES. PARAGRAFO. IGUALMENTE QUEDA FACULTADO PARA ACEPTAR Y REPRESENTAR A TECNOQUIMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ORGANOS EQUIVALENTES O SIMILARES, EN LOS PROCESOS QUE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE LAS ENTIDADES PERTINENTES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES. 7o.) REPRESENTAR 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 MAYO DE 1995, NOTARIA DECIMA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 24 DE SEPTIEMBRE DE 2003 BAJO EL NRO. 134 DEL LIBRO V SE CONFIERE PODER ESPECIAL A ANTONIO JAIRO RAMIREZ ECHAVE, ABOGADO TITULADO Y EN EJERCICIO, CON TARJETA PROFESIONAL No. 58.401 DEL MINISTERIO DE JUSTICIA, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 16.741.040 DE CALI PARA QUE REPRESENTAR A TECNOQUIMICAS S.A., EN LOS SIGUIENTES ACTOS: A) SOLICITAR Y ADELANTAR ANTE EL INSTITUTO COLOMBIANO AGROPECUARIO TODOS LOS TRAMITES ATINENTES A LA OBTENCION DE LICENCIAS DE VENTA Y LICENCIAS DE FUNCIONAMIENTO, RENOVACIONES, CERTIFICACIONES, AMPLIACIONES, INSCRIPCIONES Y MODIFICACIONES EN GENERAL; B) TODOS LOS TRAMITES ANTE EL INVIMA ATINENTES A LA OBTENCION DE REGISTRO SANITARIO, RENOVACION DEL MISMO, REFORMULACIONES, ADICIONES DE NUESTRA LINEA DE PRODUCTOS, CAMBIOS DE TITULAR Y DE FABRICANTE, CESIONES, CERTIFICACIONES DE FORMULA Y EXCLUSIVIDAD, MODIFICACIONES DE FABRICAR Y VENDER A IMPORTAR Y VENDER Y VICEVERSA, E IGUALMENTE CERTIFICACIONES SOBRE LA LINEA COMPLETA DE NUESTROS PRODUCTOS, A CUYO OBJETO LO FACULTO PARA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS.

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Operacion : 02CP20827018 PAGINA No. 13

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 DICIEMBRE DE 2004 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 17 DE ENERO 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 ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMA LA PERSONERIA A 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 CUMPLIMIENTO DE OBLIGACIONES EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER. EL APODERADO SE CE?IRA RIGUROSAMENTE A LOS TERMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TERMINO INDEFINIDO Y CUALQUIER MODIFICACION O REVOCATORIA SE HARA EXPRESAMENTE POR ESCRITURA PUBLICA.

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CAMARA DE COMERCIO DE CALI

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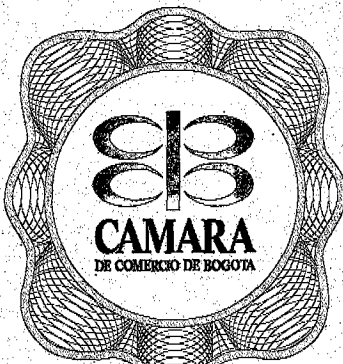
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CERTIFICA:

QUE POR ESCRITURA NRO. 4265 DEL 16 DE SEPTIEMBRE DE 2005 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE OCTUBRE DE 2005 BAJO EL NRO. 168 DEL LIBRO V EL SEÑOR JUAN BAPTISTA DE LOS RIOS GUTIERREZ MAYOR DE EDAD, DOMICILIADO EN CALI, IDENTIFICADO CON LA CEDULA DE CIUDADANIA NUMERO 17108621 DE BOGOTA, QUIEN ACTUA EN SU CALIDAD DE REPRESENTANTE LEGAL DE TECNOQUIMICAS S. A. SOCIEDAD COMERCIAL ORGANIZADA Y EXISTENTE CONFORME A LAS LEYES COLOMBIANAS, CON DOMICILIO Y SEDE PRINCIPAL EN CALI. EN DICHA CONDICION CONFIERE PODER AMPLIO Y SUFICIENTE A LAS SIGUIENTES PERSONAS: CLAUDETTE VERNOT HERNANDEZ ABOGADA TITULADA Y EN EJERCICIO, IDENTIFICADA CON LA CEDULA DE CIUDADANIA No. 51722517 DE BOGOTA, PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADO No. 57111 DEL C.S. DE LA J., ANDRES FELIPE ZAPATA OCAMPO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79598546 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 107240 DEL C.S. DE LA J. Y JUAN MANUEL SERRANO CASTILLO, IDENTIFICADO CON LA CEDULA DE CIUDADANIA No. 79875670 DE BOGOTA, PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No. 124953 DE C.S. DE LA J., TODOS CON DOMICILIO EN LA CIUDAD DE BOGOTA, D.C., PARA QUE EN NOMBRE DE MI REPRESENTADA ACTUEN EN TODOS LOS ASUNTOS DE PROPIEDAD INTELECTUAL Y LOS DERIVADOS DE ELLA, CON FACULTAD PARA RECIBIR NOTIFICACIONES, NOMBRAR APODERADOS JUDICIALES O EXTRAJUDICIALES EN ESTOS ASUNTOS.

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

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CERTIFICADO NACIONAL
CAMARA DE COMERCIO DE CALI
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Operacion : 02CP20827018 PAGINA No. 15

LICENCIAS DE FUNCIONAMIENTO, REGISTROS SANITARIOS, AUTORIZACION DE CERTIFICADOS DE LIBRE VENTA, AUTORIZACION DE PUBLICIDAD ANTE EL MINISTERIO DE PROTECCION SOCIAL O EL INVIMA O ANTE CUALQUIER AUTORIDAD SANITARIA; H) OBTENCION DE CERTIFICADOS DE CARENCIA DE INFORMES POR TRAFICO DE ESTUPEFACIENTES. RENOVACIONES, AUTORIZACIONES EXTRAORDINARIAS ANTE LA DIRECCION NACIONAL DE ESTUPEFACIENTES O EL CONSEJO NACIONAL DE ESTUPEFACIENTES; I) SOLICITUD DE AUTORIZACIONES PARA PROMOCIONES, RIFAS Y JUEGOS ANTE ETESA O ANTE LAS AUTORIDADES COMPETENTES DEL ORDEN LOCAL, DISTRITAL O DEPARTAMENTAL; Y EN GENERAL CUALQUIERA OTRA PETICION ANTE LAS AUTORIDADES ADMINISTRATIVA, ASI COMO PARA NOTIFICARSE DE CUALQUIER PROVIDENCIA Y RENUNCIAR A TERMINOS. EN TODOS LOS ASUNTOS ARRIBA DETERMINADOS LA APODERADA QUEDA FACULTADA PARA SUSTITUIR TOTAL O PARCIALMENTE ESTE MANDATO, TRANSIGIR, CONCILIAR EXTRAJUDICIAL O JUDICIALMENTE, ADMITIR LOS HECHOS DEL PROCESO PERO NO PARA CONFESAR, DESISTIR, CANCELAR, RECIBIR, RENUNCIAR Y RATIFICAR LOS ACTOS DE AGENTES OFICIOSOS.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 22 DE MAYO DE 2008 DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE JUNIO DE 2008 BAJO EL NRO. 90 DEL LIBRO V Y MODIFICADO POR DOCUMENTO PRIVADO DE FECHA 18 DE JULIO DE 2008, INSCRITA EN LA CAMARA DE COMERCIO EL 08 DE AGOSTO DE 2008 BAJO EL NRO. 151 DEL LIBRO V, SE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A LOS SIGUIENTES FUNCIONARIOS DE LA EMPRESA:

1. ANA MARZA ALVAREZ R., CON C.C. 31.170.896 DE CALI Y JORGE ENRIQUE GIRALDO, CON C.C. 16.784.794 DE CALI, OBRARAN COMO APODERADOS ESPECIALES PARA EL DESARROLLO DE LAS SIGUIENTES FACULTADES:

- A. SUSCRIBIR LOS CONTRATOS DE TRABAJO, SUS MODIFICACIONES Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE A TECNOQUÍMICAS S.A.
- B. SUSCRIBIR CONTRATOS DE APRENDIZAJE Y PASANTIAS ASI COMO SUS MODIFICACIONES Y ADICIONES.
- C. SUSCRIBIR ACUERDOS CON LOS EMPLEADOS DE LA SOCIEDAD.
- D. COMPARECER DIRECTAMENTE U OTORGAR PODER PARA ATENDER RECLAMACIONES Y PROCESOS DE ORDEN LABORAL BIEN SEA DE CARÁCTER ADMINISTRATIVO O JUDICIAL ANTE LAS OFICINAS REGIONALES DE TRABAJO, MINISTERIO DE LA PROTECCIÓN SOCIAL Y ANTE CUALQUIER OTRA AUTORIDAD O ENTIDAD ANTE LA QUE SE INICIE Y TRAMITE PROCEDIMIENTOS DE CARÁCTER LABORAL O RELACIONADOS CON TEMAS DE LA SEGURIDAD SOCIAL.
- E. FIRMAR TODOS LOS DOCUMENTOS Y ATENDER TODOS LOS TRÁMITES ANTE LAS CAJAS DE COMPENSACIÓN FAMILIAR, EMPRESAS PRESTADORAS DE SERVICIOS DE SALUD (EPS), FONDOS DE PENSIONES Y CESANTÍAS, ADMINISTRADORA DE RIESGOS PROFESIONALES (ARP), INSTITUTO DE LOS SEGUROS SOCIALES (ISS). ESTA FACULTAD TAMBIÉN COMPRENDE

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CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado 11:48:54

Operacion : 02CP20827018 PAGINA No. 16

LA DESIGNACION DE APODERADOS.

F. ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, DECLARACIONES DE PARTE Y RENDICION DE TESTIMONIOS DENTRO DE LOS PROCESOS DE LA JURISDICCION LABORAL Y TRAMITES ADMINISTRATIVOS, CUANDO ELLO SEA REQUERIDO.

G. RESPONDER LAS DEMANDAS DE TUTELA DIRECTAMENTE O A TRAVES DE APODERADO ESPECIAL.

H. SUSCRIBIR LOS CONTRATOS DE TODO TIPO CON ENTIDADES EDUCATIVAS DE TODO ORDEN, SIN LIMITACION DE CUANTIA.

I. SUSCRIBIR LOS DOCUMENTOS Y ESCRITURAS DE DONACION QUE SEAN AUTORIZADAS POR LA JUNTA DIRECTIVA, SIN LIMITACION ALGUNA.

J. SUSCRIBIR TODOS LOS CONTRATOS DE CONSTRUCCION, INSTALACION, SERVICIOS, REPARACIONES Y ADECUACIONES QUE SE REALICEN Y PRESTEN EN LA PLANTA Y SEDE ADMINISTRATIVA DE TECNOQUIMICAS S.A. LOCALIZADAS EN CALI, HASTA POR LA SUMA EQUIVALENTE A TRESIENTOS (300) SALARIOS MINIMOS LEGALES MENSUALES, DARLOS POR TERMINADO POR CUALQUIER CAUSA, PRESENTAR RECLAMOS ANTE LAS COMPAÑIAS ASEGURADORAS, EXIGIR EL PAGO DE MULTAS E INDEMNIZACIONES DE CUALQUIER TIPO QUE ESTEN PACTADAS EN LOS RESPECTIVOS CONTRATOS Y EL CUMPLIMIENTO DE ELLOS.

K. ANTE EL MINISTERIO DEL MEDIO AMBIENTE Y ORGANISMOS DE CONTROL AMBIENTAL DEL ORDEN NACIONAL, DEPARTAMENTAL Y MUNICIPAL O DISTRITAL, FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TRAMITES QUE LA SOCIEDAD TECNOQUIMICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARACTER JUDICIAL O GUBERNATIVO.

L. SUSCRIBIR LOS CONTRATOS DE PRENDA SOBRE VEHICULOS DE PROPIEDAD DE TERCEROS PARA RESPALDAR LOS PRESTAMOS QUE LA EMPRESA OTORQUE Y TODO LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA SU FORMALIZACION ANTE LAS SECRETARIAS DE TRANSITO Y/O MOVILIDAD DE LOS RESPECTIVOS MUNICIPIOS. ESTE PODER TAMBIEN COMPRENDE LA CANCELACION DE LAS PRENDAS Y LA FIRMA DE TODOS LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA TAL FIN.

M. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS ANTE CUALQUIER AUTORIDAD.

PARAGRAFO I. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRA LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARACTER JUDICIAL, GUBERNATIVO, TRIBUNALES DE ARBITRAMIENTO Y RECLAMOS ANTE LAS COMPAÑIAS ASEGURADORAS.

PARAGRAFO II. LOS APODERADOS EJERCERAN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACION.

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Operacion : 02CP20827018 PAGINA No. 17

2. JORGE ENRIQUE ARIZA BERNAL, IDENTIFICADO CON LA C?DULA DE CIUDADAN?A NO. 19.494.493 DE BOGOT?, PARA EL EJERCICIO DE LAS SIGUIENTES FACULTADES:

A. ANTE EL MINISTERIO DEL MEDIO AMBIENTE: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TR?MITES QUE LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, AS? COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O GUBERNATIVO.

B. ANTE LA SUPERINTENDENCIA DE VIGILANCIA: FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, OTORGAR PODERES, RENDIR DECLARACIONES, ATENDER VISITAS, FIRMAR LAS ACTAS CORRESPONDIENTES Y NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TR?MITES QUE LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, AS? COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O GUBERNATIVO.

C. ANTE EL FONDO NACIONAL DE ESTUPEFACIENTES Y DIRECCI?N NACIONAL DE ESTUPEFACIENTES FORMULAR SOLICITUDES, SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE REQUIERAN PRESENTAR, RENDIR DECLARACIONES, NOTIFICARSE DIRECTAMENTE O POR MEDIO DE APODERADO, EN TODOS LOS TR?MITES QUE LA SOCIEDAD TECNOQU?MICAS S.A. REQUIERA ADELANTAR ANTE LAS CITADAS ENTIDADES, SUSCRIBIR LAS ACTAS DE VISITA, Y DESIGNAR APODERADOS PARA NOTIFICARSE DE ACTOS ADMINISTRATIVOS, INICIAR O RESPONDER PROCESOS DE CAR?CTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

D. EN TODO LO RELACIONADO CON LOS TR?MITES DE IMPORTACIONES Y EXPORTACIONES, SEG?N SE INDICA:

I. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS ADMINISTRACIONES DE ADUANAS DE LA DIRECCI?N DE IMPUESTOS Y ADUANAS - DIAN - AS? COMO RENDIR DECLARACIONES, ATENDER VISITAS E INSPECCIONES Y FIRMAR LAS CORRESPONDIENTES ACTAS ATENDER DIRECTAMENTE, CUANDO ELLO SEA REQUERIDO Y EN GENERAL OBRAR COMO APODERADO ESPECIAL ANTE LAS AUTORIDADES ADUANERAS EN TODAS LAS OPERACIONES RELACIONADAS CON EL COMERCIO EXTERIOR.

II. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS SOCIEDADES PORTUARIAS DE BUENAVENTURA, CARTAGENA Y BARRANQUILLA, AS? COMO RESPONDER Y ATENDER LOS TR?MITES DIRECTAMENTE O A TRAV?S DE APODERADOS.

III. OTORGAR PODERES ESPECIALES Y GENERALES, OTORGAR GARANT?AS Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS NAVIERAS Y EMPRESAS ADMINISTRADORAS DE CONTENEDORES PARA EL MANEJO Y RETIRO DE ELLOS.

IV. OTORGAR PODERES ESPECIALES Y GENERALES A LAS SOCIEDADES DE INTERMEDIACI?N ADUANERA - SIA - Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN

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Operacion : 02CP20827018 PAGINA No. 18

DE ACUERDA CON LA NORMATIVIDAD LEGAL SOBRE LA MATERIA.

V. SUSCRIBIR LAS CARTAS DE ANTINARCOTICOS QUE SE PRESENTAN ANTE LA POLICIA AEROPORTUARIA BIEN DIRECTAMENTE O AUTORIZANDO A LOS JEFE DE BODEGA DE YUMBO Y JAMUNDI PARA RESEGUIR TRAMITE DOCUMENTOS DENTRO DE LOS TRAMITES DE EXPORTACIONES O REEMBARKES DE MERCANCIAS, Y EN GENERAL ATENDER TODAS LAS DILIGENCIAS DIRECTAMENTE U OTORGAR PODER AUN TERCERO.

D. SUSCRIBIR CONTRATOS DE CONSTRUCCION Y DE OBRA QUE SE REALICEN Y PRESTEN EN LAS PLANTAS DE TECNOQUIMICAS S.A. LOCALIZADAS EN JAMUNDI, YUMBO Y VILLA RICA (DEPARTAMENTO DEL CAUCA EN EL CONJUNTO INDUSTRIAL PARQUESUR) HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS MINIMOS LEGALES MENSUALES.

E. SUSCRIBIR CONTRATOS, SIN LIMITACION DE CUANTIA QUE TENGA QUE VER CON LA ADQUISICION DE EQUIPO Y MAQUINARIA, REPARACION, ADECUACION, INSTALACION, SERVICIOS TECNICOS Y DE ASESORIA.

E. SUSCRIBIR CONTRATOS DE FABRICACION CON TERCEROS BIEN SEA QUE TECNOQUIMICAS OBRE COMO FABRICANTE O COMO PROPIETARIO.

PARAGRAFO. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRA LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARACTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

3. MARA TERESA GONZALEZ DE GUZMAN, IDENTIFICADA CON LA Cedula de Ciudadania NO. 31.238.104 DE CALI, CARLOS ARTURO PEÑA NIETO IDENTIFICADO CON LA Cedula de Ciudadania NO. 19.483.439 DE BOGOTA Y ANGELA MARA CORREA CARDONA IDENTIFICADA CON LA Cedula de Ciudadania NO. 66.835.555 DE CALI, LA PRIMERA COMO PRINCIPAL, EL SEGUNDO COMO PRIMER SUPLENTE Y LA TERCERA COMO SEGUNDA SUPLENTE, PARA QUE REPRESENTEN A TECNOQUIMICAS S.A. EN:

A. EN TODOS LOS ASUNTOS CAMBIARIOS, CON FACULTAD PARA FIRMAR DECLARACIONES DE CAMBIOS SEA POR CREDITOS EN MONEDA EXTRANJERA, POR MOVIMIENTOS DE LA CUENTAS CORRIENTES DE COMPENSACION, IMPORTACIONES DE BIENES Y SERVICIOS, TRANSFERENCIAS Y OTROS CONCEPTOS, REGISTRO DE PRESTAMOS EN MONEDA EXTRANJERA OTORGADOS A LA EMPRESA EN SU CONDICION DE RESIDENTE Y TODOS AQUELLOS DOCUMENTOS, DECLARACIONES O RESPUESTAS A REQUERIMIENTOS QUE DEBAN HACERSE ANTE EL BANCO DE LA REPUBLICA U OTRAS ENTIDADES GUBERNAMENTALES RESPECTO DE OPERACIONES EN EL MERCADO CAMBIARIO.

LOS APODERADOS SUSCRIBIRAN TODOS LOS DOCUMENTOS Y REALIZAR TODOS LOS ACTOS QUE OBLIGUEN A LA SOCIEDAD ANTE LAS AUTORIDADES CAMBIARIAS, PUDIENDO IGUALMENTE NOTIFICARSE DE TODAS LAS ACTUACIONES, ACTOS ADMINISTRATIVOS, DILIGENCIAS O GESTIONES RELACIONADAS O QUE SE DERIVEN DE DICHA ACTIVIDAD Y EN GENERAL, PARA QUE ASUMAN LA PERSONERIA A NOMBRE DE TECNOQUIMICAS S.A. BIEN SEA DIRECTAMENTE O A TRAVES DE APODERADO, SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN NINGUN CASO QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS

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CERTIFICADO NACIONAL
CAMARA DE COMERCIO DE CALI
Fecha : 20080827 Hora Certificado 11:48:54
Operacion : 02CP20827018 PAGINA No. 19

DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CAR?CTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER.

B. EN RELACI?N CON SECTOR FINANCIERO:

I. SUSCRIBIR LOS CONTRATOS DE CR?DITO Y LEASING CON LOS BANCOS, ENTIDADES FINANCIERAS, COMPA??AS DE FINANCIAMIENTO COMERCIAL, DE ACUERDO CON LOS CUPOS FIJADOS POR LA JUNTA DIRECTIVA, AS? COMO LOS PAGAR?S, DE LOS CONTRATOS DE GARANT?A PRENDAR?A E HIPOTECARIA, LA CONFIRMACI?N DE FORWARDS Y TODOS LOS DEM?S DOCUMENTOS QUE SEAN REQUERIDOS PARA LA CULMINACI?N Y FORMALIZACI?N DE ESTOS TR?MITES.

ESTAS FACULTADES IGUALMENTE APLICAN PARA TODOS LOS CR?DITOS QUE OTORQUE EL BANCO DE COMERCIO EXTERIOR DE COLOMBIA - BANCOLDEX.

II. SUSCRIBIR LOS FORMATOS Y CONTRATOS DE APERTURAS DE CUENTAS CORRIENTES, AHORROS, SERVICIOS DE BANCA VIRTUAL, LOS FORMATOS DE PROVEEDORES PARA PAGOS POR TRANSFERENCIA ELECTR?NICA Y LOS FORMULADOS ?NICOS DE CONOCIMIENTO DE PERSONA JUR?DICA QUE EXIGE EL SECTOR FINANCIERO.

III. SUSCRIBIR LAS LETRAS DE COBRANZA Y LAS CARTAS DE CR?DITO.

C. SOLICITAR TIDIS Y FIRMAR TODOS LOS DOCUMENTOS RELACIONADOS CON ESTE TR?MITE.

D. EN RELACI?N CON LA COMPA??AS ASEGURADORAS.

I. SUSCRIBIR DOCUMENTOS DE RECLAMACI?N Y OTORGAR PODERES PARA QUE COMPAREZCAN A LAS AUDIENCIAS DE RECLAMACIONES, AS? COMO LOS DOCUMENTOS DE TRANSACCI?N. ESTAS FACULTADES SE OTORGAN SIN LIMITACI?N DE CUANT?A.

II. SUSCRIBIR LAS CARTAS DE NO RECLAMACI?N A LAS COMPA??AS ASEGURADORAS POR OCURRENCIA DE SINIESTROS Y LAS RESPECTIVAS CONSTANCIAS.

III. SUSCRIBIR LOS DOCUMENTOS REQUERIDOS POR EL SISTEMA DE INFORMACI?N PARA LA PREVENCI?N DE LAVADO DE ACTIVOS (SIPLA).

E. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS.

PAR?GRAFO 1. 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:

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COLOMBIANO
A LA CALIDAD
DE LA GESTION

IMPRESO POR DAMAGANO S.A. NT. 180.033.7116 08/01/0039

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado 11:48:54

Operacion : 02CP20827018 PAGINA No. 20

A. OTORGAR PODER Y CONSTITUIR MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON LAS DEUDAS A FAVOR DE TECNOQUIMICAS S. A.

B. SUSCRIBIR LOS CONTRATOS DE ARRENDAMIENTO DE INMUEBLES, SU MODIFICACION Y O TERMINACION, INVENTARIOS Y ANEXOS PERTINENTES, BIEN SEA QUE LA SOCIEDAD OBRE COMO ARRENDADOR O ARRENDATARIO, SIN LIMITACION DE CUANTIA. ESTA FUNCION LA PODRA EJERCER DIRECTAMENTE O MEDIANTE LA DESIGNACION DE APODERADOS.

C. SUSCRIBIR LOS FORMATOS DE AUTORIZACION DE CREACION DE CLIENTES Y PROVEEDORES DE LA EMPRESA.

D. EN RELACION CON LOS VEHICULOS DE TODO TIPO QUE FIGUREN A NOMBRE DE TECNOQUIMICAS, 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, ASÍ COMO FIRMAR TODO TIPO DE CONTRATOS RELACIONADOS CON LOS VEHICULOS.

PARAGRAFO. EN LA ATENCION DE TODOS LOS ASUNTOS MENCIONADOS TENDRA LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARACTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

ESTOS PODERES ESTARAN VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS EXPRESAMENTE POR DOCUMENTO PRIVADO.

CERTIFICA:

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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado : 11:48:54

Operacion : 02CP20827018 PAGINA No. 22

EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LOS INTERROGATORIOS DE PARTE, A LAS DIVERSAS AUDIENCIAS, ENTRE ELLAS LAS DE CONCILIACION, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES, JUDICIALES, ADMINISTRATIVAS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS DEL ESTABLECIMIENTO CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO DEL NUMERAL PRIMERO.

4. PARA SUSCRIBIR LOS CONTRATOS DE TRABAJO Y DARLOS POR TERMINADO DEL PERSONAL VINCULADO O QUE SE VINCULE AL ESTABLECIMIENTO DE COMERCIO Y EXPEDIR CERTIFICACIONES LABORALES.

5. PARA CONSTITUIR APODERADO O APODERADOS EN DESARROLLO DE LA REPRESENTACION LABORAL, SI ASI LO CONSIDERA NECESARIO, TENIENDO SUMA DILIGENCIA PARA QUE TECNOQUIMICAS S.A., EN NINGUN CASO, QUEDE SIN LA DEBIDA REPRESENTACION EN LA SALVAGUARDIA DE SUS DERECHOS Y OBLIGACIONES LABORALES Y A ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS DILIGENCIAS DE INTERROGATORIOS DE PARTE.

6. SUSCRIBIR LOS CONTRATOS DE PRENDA SOBRE VEHICULOS DE PROPIEDAD DE TERCEROS PARA RESPALDAR LOS PRESTAMOS QUE LA EMPRESA OTORGUE Y TODO LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA SU FORMALIZACION ANTE LAS SECRETARIAS DE TRANSITO Y/O MOVILIDAD DE LOS RESPECTIVOS MUNICIPIOS. ESTE PODER TAMBIEN COMPRENDE LA CANCELACION DE LAS PRENDAS Y LA FIRMA DE TODOS LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA TAL FIN.

7. PARA QUE EN DESARROLLO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO DE COMERCIO ADQUIERA Y ENAJENE TODA CLASE DE BIENES MUEBLES CUYA FINALIDAD SEA NECESARIA PARA EL MEJOR DESEMPEÑO DE LAS ACTIVIDADES DEL ESTABLECIMIENTO HASTA POR LA SUMA QUE INDIQUE LOS MANUALES Y PROCEDIMIENTOS INTERNOS DE LA SOCIEDAD.

ESTOS PODERES ESTARAN VIGENTES HASTA TANTO SEAN REVOCADOS O MODIFICADOS EXPRESAMENTE POR DOCUMENTO PRIVADO.

CERTIFICA:

CAPITAL AUTORIZADO: \$27,200,000,000

NUMERO DE ACCIONES: 54,400,000

VALOR NOMINAL: \$500

CAPITAL SUSCRITO: \$27,123,804,000

NUMERO DE ACCIONES: 54,247,608

VALOR NOMINAL: \$500

CAPITAL PAGADO: \$27,123,804,000

NUMERO DE ACCIONES: 54,247,608

VALOR NOMINAL: \$500

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado 11:48:54

Operacion : 02CP20827018 PAGINA No. 23

CERTIFICA:

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

CONTROLANTE: TECNOQUIMICAS S.A.

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

CONTROLADA: INDUGRAFICAS S.A.

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

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

UNIDAD DE PROPOSITO Y ADMINISTRACION ENTRE TECNOQUIMICAS E INDUGRAFICAS S.A. EXISTE UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

DE IGUAL MANERA SE CONCRETA EL CONTROL ADMINISTRATIVO SOBRE LA FILIAL A TRAVES DE LA GERENCIA Y LA JUNTA DIRECTIVA CUYOS MIEMBROS PRINCIPALES HACEN PARTE IGUALMENTE DE LA JUNTA Y ADMINISTRACION DE LA MATRIZ.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DEL 17 DE NOVIEMBRE DE 2005, INSCRITO EN LA CAMARA DE COMERCIO EL 23 DE NOVIEMBRE DE 2005 BAJO EL NRO. 13.159 DEL LIBRO IX, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR TECNOQUIMICAS S.A.

CONTROLANTE: TECNOQUIMICAS S.A.

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

CONTROLADA: TECNOFAR TQ S.A.

DOMICILIO: VILLA, RICA DEPARTAMENTO DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOFAR TQ S.A. CORRESPONDEN A LA PRODUCCION Y COMERCIALIZACION DE PRODUCTOS BIOLÓGICOS, QUÍMICOS, MEDICAMENTOS Y PRODUCTOS FARMACÉUTICOS, PRODUCTOS VETERINARIOS Y AGRÍCOLAS, ALIMENTOS, COSMÉTICOS Y DE TOCADOR, PRODUCTOS DE ASEO PARA EL HOGAR Y LA FABRICACION Y DISTRIBUCION DE ENVASES PLÁSTICOS PARA TODO TIPO DE USO.

UNIDAD DE PROPOSITO Y ADMINISTRACION. ENTRE TECNOQUIMICAS Y TECNOFAR, EXISTE

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PREMIO
A LA CALIDAD
DE LA GESTION

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080827 Hora Certificado 11:48:54

Operacion : 02CP20827018 PAGINA No. 24

UNIDAD DE PROPOSITO Y DIRECCION YA QUE LOS PLANES Y OBJETIVOS DE ESTA ULTIMA ESTAN DETERMINADAS POR LA PRIMERA.

DE IGUAL MANERA SE CONCRETA EL CONTROL ADMINISTRATIVO SOBRE LA FILIAL A TRAVES DE LA GERENCIA Y LA JUNTA DIRECTIVA CUYOS MIEMBROS PRINCIPALES HACEN PARTE IGUALMENTE DE LA JUNTA Y ADMINISTRACION DE LA MATRIZ.

CERTIFICA:

QUE EL 27 DE MARZO DE 2001 BAJO EL NRO.1979 DEL LIBRO IX, SE INSCRIBIO EN LA CAMARA DE COMERCIO UN DOCUMENTO PRIVADO DE FECHA MARZO 21 DE 2001, EN LA CUAL CONSTA LA SITUACION DE CONTROL EJERCIDA POR LA SOCIEDAD TECNOQUIMICAS S.A.

MATRIZ: TECNOQUIMICAS S.A.

DOMICILIO: SANTIAGO DE CALI.

NACIONALIDAD: COLOMBIANA

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

SUBORDINADA: ADHESIVOS INTERNACIONALES S.A.- ADHINTER S.A. DOMICILIO: CALI VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA

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

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

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.7050-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS

UBICADO EN: CALLE 23 7 39 DE CALI
RENOVO POR EL AÑO 2008

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CERTIFICADO NACIONAL
CAMARA DE COMERCIO DE CALI
Fecha: 20080827 Hora Certificado: 11:48:54
Operacion: 02CP20827018 PAGINA No: 25

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO. 311234-2 ESTABLECIMIENTO DE COMERCIO: TECNOQUIMICAS
UBICADO EN: K 7 22 122 DE CALI
FECHA MATRICULA: 22 DE ABRIL DE 1992
RENOVO: POR EL 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 4 56 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: 14 DE ABRIL DE 2003
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



CERTIFICADO

DE

RENOVACION

DE

LA

SOCIEDAD

EFFECTUA

LA

RENOVACION

DE

SU

MATRICULA

MERCANTIL

EL 29 DE

MARZO

DE 2008

EL 29 DE

MARZO

DE 2008



EL 29 DE

PREMIO
COLOMBIANO
A LA CALIDAD
DE LA GESTION

CERTIFICA:

CERTIFICA:

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IMPRESO POR EMBAJEMERCA S.A. NIT. 90011116 001 01-2008

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha: 20080827 Hora: certificado 11:48:54

Operacion: 02CP20827018 PAGINA No: 26

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. DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 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 27 DIAS DEL MES DE AGOSTO DEL AÑO 2008 HORA: 11:48:11

CEIB

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178
178

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 68,472
FECHA : AGOSTO 28 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-064910- -00008-0000

Fecha: 2008-08-28 08:38:43 Dep. 2020 NUECREACION
Tra. 11 PATENTEIYII Eve: 378 FASENACIONAL
Act. 400 OPOSIOBSERVTER Folios: 85

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	4276344	27/08/2008	1,023,000.00

***** CONCEPTO *****

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

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 68,475
FECHA : AGOSTO 28 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-064910- -00008-0000

Fecha: 2008-08-28 08:36:43 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOS/OBSERVIER Folios: 85

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	4276344	27/08/2008	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.