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FORMULARIO ÚNICO DE OPOSICIÓN
2000-12

1

OPOSICIÓN 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: 10-082-162
Solicitante: SCHERING-PLOUGH HEALTHCARE PRODUCTS, INC.
Apoderado: CARLOS REYNALDO OLARTE G.

Título de la nueva creación o denominación del signo:
"FORMULACIONES FARMACEUTICAS DE FENILEFRINA Y
COMPOSICIONES PARA ABSORCION TRANSMUCOSAL"
Gaceta: 632 de 20-09-2011, Número de Publicación 1221.

3

OPOSICIÓN PRESENTADA POR:

OPOSITOR	Nombre: Tecnoquímicas S.A.	IDENTIFICACIÓN	
	Dirección: Calle 23 No. 7-39	C.C. ☐	NIT ☒
	Teléfono: (092) 882.55.55	C.E. ☐	Otro ☐
	Fax: (092) 883.88.59	Número: 890 300 466-5	
	Domicilio: Cali – Valle		
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar	IDENTIFICACIÓN	
	Dirección: Cra. 17 No. 88-23, Of. 205	C.C. ☒	NIT ☐
	Teléfono: 621.26.31	C.E. ☐	Otro ☐
	E-mail: info@reyes-abogados.com	Número: 79'152.473 de Usaquén	
	Fax: 621.25.42	TP 44655	
	Domicilio: Bogotá, D.C.		

4

FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000).

Justificación: VER ANEXO.

5

Comprobante de pago No.

11123076
11123079

(Oposición) Fecha

(Prórroga) Fecha

DC 19/2011
Dic - 19/2011

6

Anexos:

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

7

NOMBRE: JOSÉ LUIS REYES VILLAMIZAR**FIRMA:**
C.C. No. 79.152.473 T.P. 44655

REYES & REYES

A B O G A D O S

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: EXPEDIENTE 10-082-162

TÍTULO SOLICITADO: FORMULACIONES FARMACEUTICAS DE
FENILEFRINA Y COMPOSICIONES PARA
ABSORCION TRANSMUCOSAL.

PUBLICACIÓN: Gaceta 632 de 20/09/2011, número de publicación
1221.

PRIORIDAD: US 61/012,223 de 07/12/2007

SOLICITANTE: SCHERING - PLOUGH HEALTHCARE PRODUCTS,
INC.

APODERADO: CARLOS REYNALDO OLARTE GARCIA.

TRÁMITE: PRESENTACIÓN DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, en desarrollo de lo dispuesto por los artículos 42 y siguientes de la Decisión 486 de 2000 de la Comunidad Andina de Naciones, me permito solicitarle, muy respetuosamente, dar curso a la siguiente:

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **10-082-162**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos

14, 16, 18 y 20 literal d) de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer 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 y composiciones farmacéuticas carentes de nivel inventivo, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana en trámite 10-082-162 que se refiere a una composición farmacéutica que comprende fenilefrina o su sal aceptable para uso farmacéutico, donde la composición se formula para ser aplicada a la mucosa oral para permitir una absorción sistémica mejorada de la forma activa para uso terapéutico de fenilefrina; no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, y teniendo en cuenta lo revelado en la reivindicación 17 de la solicitud colombiana en cuestión, en donde se hace mención de un método para administrar sistémicamente fenilefrina, es importante indicar que esto contraviene lo dispuesto en la Decisión 486 de 2000 que literalmente refiere a que *"No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnostico aplicados a los seres humanos o a animales"*.

En un segundo aspecto, y teniendo en cuenta que en las reivindicaciones 48 y 49 la solicitud colombiana en cuestión revela la combinación farmacológica entre fenilefrina y otros principios activos, es relevante mencionar el concepto de la Doctora en Bioquímica Silvia Susana Giarcovich¹ en su opinión escrita a cerca de "Asociaciones y Patentes" en donde afirma que las asociaciones farmacológicas

¹ Profesora Regular Adjunta del Departamento de Farmacología de la Facultad de Farmacia y Bioquímica de la UBA y Directora Técnica y Gerente de Estudios Clínicos de DIFFUCAP-EURAND SACIFI

están restringidas por ciertos principios y lineamientos preestablecidos por varias entidades, puesto que dichas combinaciones deben estar bajo el precepto de eficacia, seguridad y eficiencia terapéutica, veamos:

“3.3.2. Lineamientos FDA:

A continuación se mencionarán lineamientos que la agencia sanitaria de EEUU ha establecido para el caso de los llamados “*Combination Drug Products*”:

3.3.2.1. CFR

El CFR establece la política en relación a las combinaciones de drogas a dosis fija para humanos en 21CFR300.50. Allí se establece que dos o más drogas pueden ser combinadas en una única unidad posológica cuando cada componente hace una contribución al efecto propuesto y la dosis de cada componente es tal que la combinación es segura y efectiva (se consideran casos especiales cuando se busca aumentar la seguridad y eficacia del principal componente o minimizar su potencial abuso).

3.3.2.2. Guía “OTC Combination of Drug Products” [Docket No. 78D-0322]²:

Esta guía establece en detalle la política de la agencia para combinar dos o más ingredientes activos OTC, seguros y eficaces y caracteriza diferentes tipos de asociaciones de OTC:

- Ingredientes activos de diferentes categorías terapéuticas para tratar distintos síntomas simultáneamente: Sólo se acepta esta asociación si cada ingrediente está presente dentro de su rango de seguridad y eficacia.
- Ingredientes activos de la misma categoría terapéutica que tienen distintos mecanismos de acción para tratar los mismos síntomas o condición: Sólo se acepta esta asociación si es mejor o igual que cada ingrediente solo en su dosis terapéutica y también pueden usarse a dosis subterapéuticas si corresponde.
- Ingredientes activos de la misma categoría terapéutica que tienen el mismo mecanismo de acción: Estos no deberían ser combinados a menos que haya alguna ventaja con respecto a los ingredientes simples (mayor eficacia, seguridad, aceptación del paciente o calidad de la formulación).

² Anunciada en el Federal Register (1978), Vol. 43, No. 229.

- Ingredientes considerados adyuvantes, que aumenten o alteren el efecto de otro ingrediente activo, serán, considerados ingredientes activos.

3.3.2.3. Guía Draft "Current GMP for Combination Products":

Este documento provee una guía para la industria y para el *staff* de la FDA acerca de la aplicabilidad de la cGMP para las asociaciones (*combination products*) y define a un *combination product*, de acuerdo al CFR (21CFR3.2(e)), de forma que no sólo involucra drogas sino *devices*:

Un producto combinado es un producto compuesto de cualquier combinación de una droga y un dispositivo; un producto biológico y un dispositivo; una droga y un producto biológico; o una droga, dispositivo, y un producto biológico. Bajo 21 CFR 3.2 (e), un producto de combinación incluye:

- 1. Un producto que comprende dos o más componentes regulados (i.e., droga/dispositivo, biológico/dispositivo, droga/biológico, o droga/dispositivo/biológico) que son combinados físicamente, químicamente, o de otra forma, o mezclados y producidos como una entidad única;*
- 2. Dos o más productos separados, empaquetados juntos en un solo paquete, o como una unidad comprendiendo droga y productos del dispositivo, dispositivo y productos biológicos, o biológico y productos de droga;*
- 3. Una droga, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo a su plan de investigación o el etiquetado propuesto, es destinado para utilizarse únicamente con una droga, dispositivo, o producto biológico aprobada especificada individualmente, dónde al mismo tiempo ambos son deben estar aceptados para la indicación o efecto y donde, luego de la aprobación del producto propuesto, el etiquetado del producto aprobado necesitaría ser cambiado (e.g., para reflejar un cambio en la indicación, forma farmacéutica, dosis, ruta de administración, cambio significativo en la posología); ó*
- 4. Cualquier droga en investigación, dispositivo, o producto biológico empaquetado separadamente que, de acuerdo al etiquetado propuesto es para utilizarse únicamente con otra droga en investigación especificada, dispositivo, o producto biológico, dónde a la vez se requiere que ambos sean aceptados para la misma indicación, uso y efecto.*

Además, dentro de esta guía es muy interesante el concepto de "parte constitutiva de un *combination product*" porque especifica su identidad regulatoria como droga, *device* o producto biológico.

3.3.2.4. Guía Draft "Combination Products Timeliness of Premarket Reviews":

Esta guía provee información a un postulante a reclamar la resolución de una disputa acerca de la duración de la revisión de una postulación referida a un producto combinado. Es una guía referida simplemente a un problema administrativo que demuestra cuán regulado se halla este ámbito que tiene una oficina destinada, la Office of Combination Products.

3.3.3. Lineamientos EMEA: Guía "Fixed Combination Medicinal Products":

Esta guía propone evaluar las potenciales ventajas de la asociación en cuanto a mejoramiento de la relación riesgo/beneficio y a simplificación de la terapia. Asimismo, establece criterios a respetar y requisitos a cumplimentar, tanto generales como particulares. Dentro de los particulares hace especial referencia a:

- La indicación.
- Los estudios farmacodinámicos y farmacocinéticos.
- Eficacia y Seguridad: En este caso diferencia dos escenarios concretos:
 - a) *Cuando la combinación fija corresponde exactamente a combinaciones que están ya en uso difundido, un análisis de los datos bibliográficos bien fundamentados debería ser presentado. Con tal que los datos estén bien documentados, este análisis puede ser útil en reducir la cantidad de ensayos clínicos a ser realizada y podría facilitar la selección de dosis para cada sustancia y el rango de dosis propuesto en la combinación fija.*
 - b) *Cuando la combinación fija es esencialmente nueva (las sustancias activas no son usualmente combinadas, la composición cuantitativa es inusual entre sustancias usualmente combinadas o una sustancia enteramente nueva), los datos necesarios son similares a los de una nueva entidad química en la situación donde la combinación fija será propuesta (primero línea o segunda de la línea de terapia). La existencia de experiencia con las sustancias debería ser tomada en cuenta.*

y especifica Régimen de dosis y Composición, Ensayos Terapéuticos y Aspectos de Seguridad.

- Paquetes combinados de diferentes productos medicinales para administración simultánea o secuencial.

Conclusión:

Las diferentes agencias sanitarias a nivel internacional han regulado fuertemente el registro de asociaciones de forma de garantizar la seguridad y eficacia de las mismas y la buena calidad en su elaboración. Todo estudio, investigación o análisis

derivados de estos requisitos representan procedimientos de rutina y no originales ideas llevadas a la práctica."

Además, se puede considerar que todo efecto sinérgico o terapéutico entre fármacos no se refiere propiamente a una invención, sino que corresponde mejor a la categoría de un descubrimiento, dado que dicho efecto sinérgico o terapéutico conseguido mediante la combinación de fármacos ocurre dentro del organismo y se hace evidente a través de los respectivos ensayos preclínicos y/o clínicos por los que todo fármaco o combinación de fármacos se deben evaluar. Así mismo es importante volver a enfatizar en que la combinación de fármacos para tratar ciertas patologías, hace parte de las actividades de la profesión médica, y no de las actividades industriales.

Finalmente, existen documentos que revelan con anterioridad varias de las características técnicas reivindicadas por la presente solicitud, con lo cual se puede desvirtuar el nivel inventivo de la misma, veamos:

La patente americana US 2002/022057 publicada el 21 de febrero de 2002 revela:

An alternate drug delivery system for dissolution of pharmaceuticals in the mouth wherein a therapeutically effective amount of a drug is encapsulated using an encapsulation method. Encapsulation reduces the perceived off flavors of

drugs, allowing the active components to dissolve pleasantly in the mouth. This allows more rapid absorption of the active compounds through the oral cavity compared to traditional tablets, which require breakdown and absorption in the gastrointestinal tract. The delivery system can be incorporated into a variety of applications, such as breath mint tablets or chewing gum. Benefits of this invention include portability and the ability to take pharmaceuticals without water and without the off taste of chewable tablets, thereby leading to increased patient compliance.

(...)

[0002] This invention relates to a new delivery system for pharmaceuticals using encapsulation technology and a process for its preparation. In particular, the invention relates to

a process for preparing products that are capable of dissolving in the mouth. This leads to more rapid absorption of the pharmaceutical components than traditional delivery methods. The compositions are designed to mask the taste associated with many drugs and provide a pleasant flavor sensation.

(...)

[0023] Sublingual and buccal administrations allow the drug to be absorbed in the mucosal lining of the mouth, either under the tongue or in the area between the cheek and gum. The traditional forms of administration are compressed buccal tablets and compressed sublingual tablets.

(...)

[0026] Absorption of therapeutic agents through the mouth can be very effective, but is utilized by only a few types of drugs. Lozenges commonly include medicaments that require contact with the mucous membrane, such as decongestants and cough suppressants. It is difficult to include many medicines into traditional hard candy lozenges because of the high temperature used (135 to 150°C.), poor solubility of many drugs, and their high melting points. Furthermore, the moisture content of hard candies (0.5 to 1.5%) and their hygroscopic characteristics cause many medicines to degrade.

(...)

[0033] The encapsulated components can be used in a variety of applications, including but not limited to, compressed tablets and chewing gum.

(...)

[0034] Many kinds of therapeutic agents can be utilized in the present invention, such as anesthetics, decongestants, antihistamines, antitussives, antibiotics, analgesics, alkaloids

(...)

[0041] The process of encapsulating therapeutic substances can be achieved using many different types of technology, since many known encapsulation processes can create a palatable product that can be absorbed in the mouth. The critical component is to encapsulate the drug and flavors into a stable form that protects the active component from chemical interactions and reactions caused by environmental abuses, such as temperature fluctuations, moisture, and light.

(...)

[0042] Microencapsulation technologies currently employed by the food, flavor, and pharmaceutical industries are summarized by Dziezak (1988), Heath (1978), and Tan (1995). These include spray drying, air suspension coating, extrusion, spray cooling and chilling, emulsion and microemulsion, adsorption, centrifugal extrusion, rotational suspension separation, rotogranulation, coacervation, continuous crystallization or cocrystallization, inclusion, and liposome formation. There are benefits and negatives associated with each of these technologies that should be considered when selecting the appropriate encapsulation technology for a certain medicament. The method of encapsulation used is not narrowly critical to the invention. Any encapsulation method now known or any equivalent encapsulation method to be known in the future can be used to prepare encapsulated therapeutic substances as disclosed herein.

(...)

[0063] This example describes the encapsulation of phenylephrine hydrochloride via extrusion. Phenylephrine hydrochloride stimulates the sympathetic nervous system, lowers blood pressure, and constricts blood vessels. The encapsulation process detailed in Example Five is repeated using 36.0% saccharose, 36.0% maltodextrin, 0.13% of phenylephrine hydrochloride and 4.2% of water. A blend of 75 mg of the encapsulated drug and 675 mg of the tableting sugar (Di-Pac®) can be compressed into tablets that yield 10 mg phenylephrine hydrochloride.

(...)

27. The dry particulate drug delivery system of claim 14, ~~wherein phenylephrine hydrochloride is~~ encapsulated by said cocrystallization method.

Por su parte la patente americana US 2007/003627 publicada el 21 de junio de 2007 revela:

A mixed-release tablet or capsule formulation including vehicles for the delivery of a plurality of drugs in various combinations of immediate release, extended release, and/or delayed release modes over a predetermined time period have been developed, which provide for controlled release not just of the drugs, but controlled release that is designed to create more effective coordination between the drugs being delivered. The drugs can be any medically and/or physiologically appropriate combination of drugs and active ingredients, preferably decongestant drugs, antihistamines, expectorants, antitussives, cough suppressants, and drying agents.

(...)

[0011] The pharmaceutical formulation may include a combination of the anti-tussive, anti-histamine and drying agent; a combination of the decongestant and drying agent; a combination of the decongestant and cough suppressant; a combination of the expectorant and cough suppressant; or a combination of the expectorant and anti-tussive in a capsule, tablet, oral rapid dissolving tablet, softgel, gelcap, film, gum, pastille, lozenge, disk, or wafer form. The antitussives,

(...)

Oral Rapid Dissolving Tablets

[0096] This example illustrates the making of an oral rapid dissolving tablets prepared from sustained release granules

containing chlorpheniramine maleate (8 mg) and phenylephrine HCl (20 mg), and methscopolamine nitrate (2.5 mg). Chlorpheniramine maleate, 90K Kollidon® and Cab-o-sil were mixed and then coated with SURELEASE® to form the first sustained release granules. Delayed release (second) granules having methscopolamine as the active drug and containing 90F Kollidon, Cab-041 were coated with Eudragit® RS or Eudragit® RL or combinations thereof. The coated granules achieved a delayed release of methscopolamine for about 2-4 hours compared to the other actives.

Mixtures of first sustained release and second delayed release granules were combined with a fast-dissolving excipient systems, (F-Melt, Fuji Chemical Industry) or Pharmaburst™ (SPI Pharmaceuticals), and then directly compressed into tablets. These tablets dissolved in the oral cavity within 30 seconds. Typically, the final rapid dissolve formulation contained fast-dissolving excipients (-40-70% by weight), sustained and delayed release granules containing actives (-30-60% by weight) and magnesium stearate (-0.4%)

(...)

Como se puede apreciar claramente, en estas anterioridades ya se revelaba la elaboración de formulaciones para ser aplicadas a través de la mucosa oral, en donde dicha aplicación consiste en una rápida disolución de la formulación farmacéutica, especialmente de fenilefrina y otros fármacos descongestionantes, antitusivos y antihistamínicos. Específicamente se hace mención de la microencapsulación de fenilefrina para la elaboración de dichas formulaciones, estrategia tecnológica que se utiliza de la misma forma en la solicitud colombiana en trámite.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

VI. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18 y 20 literal d) (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 tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- Todos los documentos anunciados en el acápite de Fundamentos de la Oposición.

VII. ANEXOS

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

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

VIII. NOTIFICACIONES

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

Señor Superintendente,


JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén
T.P.A. 44.655 de C.S.J.



US 20020022057A1

15

(19) **United States**

(12) **Patent Application Publication**
Batthey et al.

(10) **Pub. No.: US 2002/0022057 A1**

(43) **Pub. Date: Feb. 21, 2002**

(54) **ORAL DELIVERY OF PHARMACEUTICALS
VIA ENCAPSULATION**

(76) **Inventors: Alyce S. Batthey, West Springfield, MA
(US); Jacob Batthey, West Springfield,
MA (US)**

Correspondence Address:
Parker & DeStefano
Suite 300
300 Preston Avenue
Charlottesville, VA 22902 (US)

(21) **Appl. No.: 09/931,793**

(22) **Filed: Aug. 17, 2001**

Related U.S. Application Data

(63) **Non-provisional of provisional application No.
60/225,877, filed on Aug. 17, 2000.**

Publication Classification

(51) **Int. Cl.⁷ A61K 9/14; A61K 9/16**

(52) **U.S. Cl. 424/490; 514/282; 514/270;
514/210.09**

(57) **ABSTRACT**

An alternate drug delivery system for dissolution of pharmaceuticals in the mouth wherein a therapeutically effective amount of a drug is encapsulated using an encapsulation method. Encapsulation reduces the perceived off flavors of drugs, allowing the active components to dissolve pleasantly in the mouth. This allows more rapid absorption of the active compounds through the oral cavity compared to traditional tablets, which require breakdown and absorption in the gastrointestinal tract. The delivery system can be incorporated into a variety of applications, such as breath mint tablets or chewing gum. Benefits of this invention include portability and the ability to take pharmaceuticals without water and without the off taste of chewable tablets, thereby leading to increased patient compliance.

ORAL DELIVERY OF PHARMACEUTICALS VIA ENCAPSULATION

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] This invention relates to a new delivery system for pharmaceuticals using encapsulation technology and a process for its preparation. In particular, the invention relates to a process for preparing products that are capable of dissolving in the mouth. This leads to more rapid absorption of the pharmaceutical components than traditional delivery methods. The compositions are designed to mask the taste associated with many drugs and provide a pleasant flavor sensation.

2. BRIEF DESCRIPTION OF THE PRIOR ART

[0003] The traditional delivery method for pharmaceutically-active compounds is a tablet or capsule which is designed to be swallowed whole and absorbed in the gastrointestinal (GI) tract.

[0004] Many drugs, including all non-steroidal anti-inflammatory drugs such as aspirin, can cause gastrointestinal upset, heartburn, indigestion, ulcers, and gastric bleeding. [Croft et al., Br. Med. J. 1:137 (1967); Petty et al., Ann. Intern. Med. 130:14-22 (1999)]. Compounds can be buffered to minimize the contact time with the stomach lining.

[0005] Many products are coated to prevent absorption in the stomach and to minimize the unacceptable taste characteristics associated with many drugs. Enteric coatings are often employed, which allow the analgesic (e.g. aspirin) to pass through the stomach and dissolve in the small intestine. The more alkaline environment of the intestines dissolves the enteric coating allowing the aspirin to be released. The result is slow and/or incomplete absorption, leading to delayed therapeutic effects.

[0006] There are many examples of enteric coatings, as summarized in U.S. Pat. No. 4,755,387. U.S. Pat. No. 3,524,910, discloses coating analgesics with ethyl cellulose in a weight amount relative to the amount of analgesic of from 1:22 to 1:50. U.S. Pat. No. 3,656,997 discloses analgesic containing gelatin capsules having a first coating of an enteric material. U.S. Pat. No. 3,691,090 discloses a method of encapsulating aspirin cores with an enteric polymer. U.S. Pat. No. 3,906,086 discloses a particle having an aspirin core and an enteric phthalate coating. U.S. Pat. No. 4,308,251 discloses aspirin tablets containing aspirin, an enteric material and an erosion promoting agent such as corn starch.

[0007] Additional references that disclose analgesic coatings include U.S. Pat. No. 2,953,497 which discloses analgesic granules having a cellulose acetate phthalate coating; U.S. Pat. No. 3,166,476 which discloses aspirin particles which have a first coating of a material such as gelatin and a second enteric coating; and British Pat. No. 1,129,811 which discloses aspirin particles which have a coating of a polysalicylide and possibly a second, unspecified coating.

[0008] The use of lipids to provide a sustained release of therapeutic agents were disclosed by U.S. Pat. No. 2,921,883 using a mixture of a lipid (e.g., glyceryl tri-dihydroxystearate) and a cellulose derivative; U.S. Pat. No. 3,147,187 using drug mixed with a fat (e.g., glyceryl tristearate), and

a swellable gum or proteinaceous material; U.S. Pat. No. 3,402,240 using lipid matrix of carnauba wax, candelilla wax, esparto wax, or ouricury wax; U.S. Pat. No. 4,132,753 using a wax-like material in conjunction with radiation heating; U.S. Pat. No. 4,375,468 using waxes, fats, cellulose esters alone or in various combinations; U.S. Pat. No. 4,483,847 using a mixture of high and low melting point lipids; U.S. Pat. Nos. 4,755,387; 5,891,476 using a wax and emulsifier; and U.S. Pat. No. 5,728,403 using an unique combination of triglycerides that melt at body temperatures and a polymer that dissolves in the acidic environment of the stomach.

[0009] Alternative delivery systems for those patients who have difficulty swallowing tablets include chewable tablets and liquid solutions. These forms are particularly beneficial to certain classes of ill people, children, elderly people, and even veterinary patients.

[0010] Chewable dosage forms for drug delivery are well known to the pharmaceutical industry. Conventional chewable tablets consist of the medicinal agent and various ingredients, such as sugars, flavors, and colors. A common problem associated with chewable tablets is the unpleasant taste of the active components. These include metallic tastes, acidity, bitterness, burning in the back of the throat, and unpleasant odors. A great deal of research has been conducted to improve the taste of chewable tablets.

[0011] Some of the research has focused around coating the unpleasant flavors. U.S. Pat. No. 4,786,502 discloses the use of lipid material to mask bad tasting drugs in chewable form. U.S. Pat. Nos. 4,609,543 and 5,320,848 disclose the use of lipid materials and special processes to provide intimate contact of the lipid with the medicament to achieve superior taste masking. U.S. Pat. No. 4,882,152 discloses a coating using glycerides, lecithin, polyoxylalkylenes, or polyalkylene glycols gelatin, sweetener, glycerin, and water. U.S. Pat. No. 4,786,508 discloses using a polymeric coating containing copolymer with residues of (meth)acrylic esters and dimethyl, aminoethyl (meth)acrylate. U.S. Pat. No. 4,894,233 discloses coating the medicament particles with a hydrophobic matrix to mask the taste of the drug. U.S. Pat. No. 4,975,270 uses elastomer-encased active ingredients dispersed in an intensely flavored chewing gum base to mask the taste of medicaments. U.S. Pat. No. 5,380,535 discloses a drug intimately dispersed or dissolved in a pharmaceutically-acceptable lipid that is soluble at room temperatures. The utilization of lipids to mask the taste of the drugs often imparts a greasy taste and dispersants, such as sugar and emulsifiers, are used to minimize this sensation. U.S. Pat. No. 5,753,255 discloses the use of tricaprin (capric triglyceride) which requires no dispersant material to produce a superior tasting tablet. U.S. Pat. No. 4,851,226 discloses coating active ingredients with a blend of cellulose acetate or cellulose acetate butyrate and polyvinylpyrrolidone. U.S. Pat. No. 5,494,681 discloses the use of a wax and hydrophobic polymer to deliver a tasteless pharmaceutical.

[0012] Another way to improve the taste of chewable tablets is to process the medicament into roto granules (U.S. Pat. No. 5,215,755) and to coat these granules with a mixture of hydroxyethyl cellulose and hydroxypropyl methylcellulose (U.S. Pat. No. 5,460,825). This disperses the medicament into smaller pieces throughout the product and reduces the perceived strength of the bitter components.

[0013] Off flavors associated with drugs can often be overpowered with strong flavors and sweeteners, as disclosed in U.S. Pat. No. 5,013,716. Taste-masking additives have also been found to minimize the perception of unpleasant components. U.S. Pat. No. 4,758,424 discloses masking a bitter tasting decongestant with a complex aluminum silicate comprised of silicon dioxide, magnesium oxide, and aluminum oxide. U.S. Pat. No. 4,632,821 discloses the use of a complex magnesium trisilicate to reduce the bitterness of decongestants. U.S. Pat. Nos. 4,971,791 and 5,286,489 disclose using a copolymer with a plurality of carboxylic acid and ester groups to create a drug-polymer matrix with an amine or amido containing active compound. U.S. Pat. Nos. 4,910,023 and 5,681,577 disclose the use of silicon dioxide to mask poor tasting drugs. U.S. Pat. No. 5,599,556 discloses the use of a prolamine coating to mask the unpleasant tastes associated with orally administered drugs.

[0014] Chewable forms of tablets are known to have a rapid onset of bioactivity compared to conventional tablets that are swallowed (U.S. Pat. Nos. 4,820,523; 6,060,078, Daruwala, 1980). This is because the active components are presented to the GI tract in smaller pieces and often times in a solution with saliva. This leads to more rapid absorption than conventional solid tablets which require disintegration and dissolution.

[0015] Liquid forms have an even faster rapid absorption rate than conventional solid delivery systems. Liquid forms include suspensions, syrups, and elixirs. A significant challenge while formulating liquid medicines includes masking the off flavors of the medicament. Furthermore, liquid medications are less portable and are inconvenient to administer.

[0016] All of these forms of swallowed medications require absorption through the stomach or intestine. Once the drug is absorbed, it passes through the portal vein, into the liver, and then to the heart and arterial circulation, which distributes the drug throughout the body. The drug is often diluted by gastrointestinal secretions and stomach contents. The drug can also interact with normal constituents of the GI tract, food stuffs, or other drugs, decreasing the absorption. Often times, the efficacy of certain drugs is reduced by the enzymes and environmental conditions of the GI tract. Furthermore, the liver, as the body's major organ of detoxification, can metabolize the drug, minimizing its therapeutic effect.

[0017] There are many occasions where the absorption rate is critical to therapeutic treatment. For example, it is widely accepted that antithrombotic agents such as aspirin can be used to treat people who are having a heart attack. Aspirin and other antithrombotic agents have been reported to inhibit cyclooxygenase, an enzyme found to induce platelet aggregation and constriction of blood vessels [Burch et al., J. Clin. Invest. 61:314 (1978); Majerus, J. Clin. Invest. 72:1521 (1983); Roth et al., J. Clin. Invest. 56:624 (1975); FitzGerald et al., J. Clin. Invest. 71:676 (1983); Preston et al., N. Engl. J. Med. 304:76 (1981)]. Soluble aspirin and mouth-dispersible aspirin has been recommended over plain aspirin or enteric-coated aspirin because of their rapid absorption rates [Muir et al., Curr Med Res Opin. 13(10):547-53 (1997)].

[0018] Examples of drug delivery systems that are not swallowed include parenteral (by injection), transdermal

(through the skin), sublingual (under the tongue), and buccal (between the cheek and gum) administration. Parenteral administration is the most rapid form since the drug is injected directly into the blood stream and does not require any absorption. This is a widely used method for many applications but is not preferred by patients for their daily medication needs, for obvious reasons.

[0019] There has been a great deal of research focusing on the transdermal administration of drugs. U.S. Pat. No. 4,654,209 describes creams containing analgesics which when applied to the skin resulted in positive blood and urine tests for the active ingredient. Topical applications of the drugs followed by absorption through the unbroken skin are usually found to be ineffective, in part because the rate of absorption or penetration through the skin is too slow to be effective and because the molecular size of the analgesics is quite large.

[0020] Compounds that enhance the rate of penetration have been proposed. U.S. Pat. No. 4,948,588 discloses percutaneous absorption accelerators using analgesics, such as morphine, codeine, and aspirin. Aprotic solvents such as dimethylsulfoxide lead to increased absorption [Scheuplein, J. Invest. Dermatol., Vol. 67, 31-38 (1976)], but produce side effects including inflammation and soreness of the skin, as well as foul breath and body odor.

[0021] U.S. Pat. No. 4,476,115 discloses an analgesic composition applied to the skin together with or subsequent to the application of a non-toxic water-soluble sulfite. Percutaneous or transdermal absorption of the analgesic was observed within a few hours of administration, usually within 20-30 minutes.

[0022] U.S. Pat. No. 6,071,896 discloses a percutaneous administration of aspirin for suppression of thromboxane levels. Aspirin is applied topically to the skin without the gastric effects normally associated with aspirin therapy. Poor bioavailability was shown by monitoring platelet cyclooxygenase activity and plasma drug levels. Aspirin applied to the skin absorbed very slowly, resulting in delayed onset of activity. Furthermore, skin reactions, including erythema and peeling, were noted in 30% of the subjects.

[0023] Sublingual and buccal administrations allow the drug to be absorbed in the mucosal lining of the mouth, either under the tongue or in the area between the cheek and gum. The traditional forms of administration are compressed buccal tablets and compressed sublingual tablets.

[0024] Lozenges are defined as flavored medicated dosage forms intended to be sucked and held in the mouth or pharynx [Drug Ther. Bull. Lozenges, Mouthwashes, and Gargles, 10:33 (1972)]. Lozenges are traditionally hard candies that provide a slow, uniform release of medicine directly onto the affected mucous membrane (Peters, 1980). The less common form of lozenges is a compressed tablet.

[0025] Drugs that can be absorbed in the mouth enter the bloodstream more rapidly and at a higher concentration than traditional swallowed tablets [Ansel, 1981; Conine and Pikal, 1980]. The mucosal lining of the mouth is highly vascular and moves the drug directly into the heart and arterial circulation without first passing through the liver.

[0026] Absorption of therapeutic agents through the mouth can be very effective, but is utilized by only a few

types of drugs. Lozenges commonly include medicaments that require contact with the mucous membrane, such as decongestants and cough suppressants. It is difficult to include many medicines into traditional hard candy lozenges because of the high temperature used (135 to 150°C.), poor solubility of many drugs, and their high melting points. Furthermore, the moisture content of hard candies (0.5 to 1.5%) and their hygroscopic characteristics cause many medicines to degrade.

[0027] Sublingual and buccal applications are even more limited and include nitroglycerin and certain steroid sex hormones. Drugs such as amphetamines, adrenaline, barbiturates, analeptics, and alkaloids such as morphine, cocaine, and codeine, have been explored (Beckett et al., 1968; Walton, 1944; Walton and Lacey, 1935).

[0028] The general application of orally absorbing drugs has not been extensively studied. It has been suggested that this is due to the bitter taste imparted by many drugs and the psychological barriers associated with holding drugs in the mouth (Ansel, 1981).

[0029] An alternative delivery system is needed that provides specific therapeutic effects without the side effects associated with current delivery forms. It would be extremely desirable to provide consumers with a portable, convenient, pleasant tasting delivery form where the therapeutic effects are faster acting than those currently on the market. Improved patient compliance is expected as a result of these benefits.

SUMMARY OF THE INVENTION

[0030] This invention provides a delivery system which allows the medicament to be absorbed in the oral cavity, leading to a more rapid response to the drug. Specific therapeutic effects, such as the analgesic and antithrombotic properties of aspirin, would be obtained without exposing the GI tract to high local concentrations of the drug. This invention provides a pleasant experience for patients on drug therapy regimens and allows patients with gastric intolerance, or duodenal or gastric ulcers to benefit from many medicines. Furthermore, this invention provides customers with a portable delivery form which is easy to administer and pleasant tasting.

[0031] In accordance with the present invention, an alternative drug delivery system is proposed that is capable of absorption in the oral cavity and masking the taste of the drug through encapsulation.

[0032] The product can be administered orally and allowed to remain in the mouth, instead of swallowing or chewing the tablet. This allows the active compounds to absorb through the lining in the oral cavity, leading to more rapid absorption than traditional delivery systems.

[0033] The encapsulated components can be used in a variety of applications, including but not limited to, compressed tablets and chewing gum.

DESCRIPTION OF THE PREFERRED EMBODIMENTS OF THE INVENTION

[0034] Many kinds of therapeutic agents can be utilized in the present invention, such as anesthetics, decongestants, antihistamines, antitussives, antibiotics, analgesics, alkaloids

(morphine, codeine, caffeine, cocaine), amphetamines, hormones (adrenaline, epinephrine), barbiturates, and analeptics. Medicines with a high oil/water partition coefficient or good oil solubility are effective to administer through oral absorption. This is because absorption through the oral mucosa is a passive diffusion of the un-ionized form of the drug from the aqueous phase (in the saliva) to the lipid phase (in the membrane) [Beckett et al., 1968].

[0035] The level of medicament is dependent on several factors, including the desired dosage, method of encapsulation, absorption characteristics, and desired tablet size. Compressed tablets are rarely greater than 25 to 30% of the final tablet weight, because of the flavor, mouth-feel, and other organoleptic issues (Peters, 1980). The benefit of the present invention is that higher levels of the drug can be used, because the encapsulation helps to mask the off flavors. An additional benefit of the present invention is that lower levels of drugs are required to achieve the same therapeutic effect because of the greater absorption rates.

[0036] The medicament(s) can be incorporated into the basic system of this invention along with flavor(s) and other optional ingredients. These include natural and artificial sweeteners, colors, preservatives, fillers, binders, lubricants, suspending agents, acids, buffers, stabilizing agents, and any other ingredients familiar to those skilled in the art of pharmaceutical and confectionery formulation.

[0037] The use of flavors to mask the off taste associated with many medicines is widespread. It has been recommended that flavors be selected that offset the tastes associated with certain drugs (Daruwala, 1980). For example, acidic or sour drugs, such as aspirin, are best masked with acidic flavors, such as citrus, berry flavors, licorice, and root beer. Bitter drugs are best masked by mint, licorice, cherry, nut, and chocolate flavors. Metallic flavors can be masked well with grape.

[0038] The use of sweeteners to mask the unpleasant taste of drugs is also widespread (Daruwala, 1980). Sweeteners such as sucrose, fructose, dextrose, lactose, mannitol, sorbitol, maltose, xylitol, saccharin and saccharin sodium, cyclamates, neotame, aspartame, sucralose, acesulfame potassium can be utilized. Artificial sweeteners often have an extremely high degree of sweetness, which comes in handy when formulating pleasant tasting products. Since only small quantities of the high intensity sweetener are required to mask very bitter components, a prohibitively large tablet is not required.

[0039] Certain sweeteners can impart their own characteristics to the product. For example, cooling sensation and smooth mouth feel are associated with tablets containing sorbitol and dextrose while those containing artificial sweeteners, such as aspartame and saccharin, can impart bitterness. A variety of masking agents are available to mask undesirable flavors. Even low levels of sodium chloride can be used to increase the sweetness perception and overcome off flavors.

[0040] The use of flavoring agents and sweeteners to mask the off taste has been criticized when making sublingual or buccal tablets (Conine and Pikal). This is because the compounds increase the flow of saliva. Certain drugs are designed not to be swallowed since the absorption rate through the GI tract can be significantly reduced or the

active components can be destroyed by the liver. This must be taken into account during the selection of the medicament, flavors and sweeteners, and the encapsulation system. This invention best serves as an alternate delivery system for those types of drugs that are currently swallowed.

[0041] The process of encapsulating therapeutic substances can be achieved using many different types of technology, since many known encapsulation processes can create a palatable product that can be absorbed in the mouth. The critical component is to encapsulate the drug and flavors into a stable form that protects the active component from chemical interactions and reactions caused by environmental abuses, such as temperature fluctuations, moisture, and light.

[0042] Microencapsulation technologies currently employed by the food, flavor, and pharmaceutical industries are summarized by Dziezak (1988), Heath (1978), and Tan (1995). These include spray drying, air suspension coating, extrusion, spray cooling and chilling, emulsion and micro-emulsion, adsorption, centrifugal extrusion, rotational suspension separation, roto granulation, coacervation, continuous crystallization or cocrystallization, inclusion, and liposome formation. There are benefits and negatives associated with each of these technologies that should be considered when selecting the appropriate encapsulation technology for a certain medicament. The method of encapsulation used is not narrowly critical to the invention. Any encapsulation method now known or any equivalent encapsulation method to be known in the future can be used to prepare encapsulated therapeutic substances as disclosed herein.

[0043] Cocrystallization is an example of a process that can be utilized to create this invention. Cocrystallization is defined as a process whereby a second ingredient is incorporated into a micro-sized sucrose crystal by the unique phenomenon of spontaneous crystallization (Rizzuto et al., 1984). Various techniques and apparatuses have been developed for carrying out the continuous crystallization of highly water-soluble solutes, such as sugar (U.S. Pat. Nos. 1,724,627, 2,160,533, 2,587,293, 3,194,682, 3,247,021, 3,365,331, 3,424,221, 3,503,803, 3,627,582 and 3,680,621). Further improvements were made to the disclosed apparatuses to decrease the cost and complexity and increase the commercial viability of cocrystallized products (U.S. Pat. Nos. 3,981,739 and 4,009,045). U.S. Pat. Nos. 4,159,210, 4,338,350, and 4,362,757 disclose applications of cocrystallized products for the food, flavor, and pharmaceutical industries.

[0044] Cocrystallization involves modifying sucrose crystals into an irregular, micro-sized agglomerated form that traps flavors or other ingredients (Chen et al., 1988). Spontaneous crystallization occurs when a supersaturated sugar solution is vigorously agitated. Adding flavors or other additives causes the mixture to crystallize and traps the components in the matrix. The methods described in U.S. Pat. No. 4,338,350 were used to create examples of this invention.

[0045] Cocrystallization leads to stable products with a very good shelf life. Other benefits include direct tableting characteristics which provide significant advantages to the candy and pharmaceutical industries (Rizzuto et al., 1984). Cocrystallization also improves the solubility, dispersability, wettability, anticaking, antiseperation, antidusting, homoge-

neity, flowability of the product. Furthermore, the medicament is evenly dispersed in micro-sized particles entrapped within the flavor/sugar matrix. As the product dissolves in the mouth, the small size of the medicament and its proximity to high sugar and flavor levels prevents the perception of any off tastes. This allows products formulated with the encapsulated medicament to be held in the mouth and absorbed in the oral cavity.

[0046] It was mentioned that the bitter taste imparted by many drugs and the psychological barriers associated with holding drugs prevents the general use of orally absorbed medicines. Lozenge formulations overcome these issues because the high sweetness and flavor levels reminds patients of candy. The present invention goes one step further by encapsulating flavor, sweetener, and medicament. This provides patients with an acceptable and even pleasant delivery form, leading to better patient compliance.

EXAMPLE 1

[0047] This example describes the encapsulation of aspirin via cocrystallization. Five hundred grams of granulated sugar and 150 grams of water were heated to 255° F. The molten sugar was transferred to a paddle mixer (Kitchen Aide) and continuously stirred. Fifty grams of granulated USP Aspirin 1020 (Rhodia, Cranbury, N.J.) was gradually added. Approximately one teaspoon (2.76 grams) of peppermint flavoring (Wilton Enterprises, Woodridge, Ill.) was added along with 10 drops of liquid blue food coloring (McCormick & Co., Hunt Valley, Md.). The flavor in combination with the vigorous mechanic agitation provides nucleation for the sucrose/aspirin mixture to crystallize. Within a couple of minutes, the syrup reached the temperature at which transformation and crystallization can begin and the mixture is converted into a powder. A significant amount of latent heat was given off during crystallization, leading to evaporation of the moisture and creation of a dry product. The product is compressible and can be formed into tablets using conventional methods known to those in the pharmaceutical and confectionery field. A 1.1 gram tablet provides 100 mg of aspirin and has a pleasant, sweet, mint character.

EXAMPLE 2

[0048] This example describes the encapsulation of caffeine via cocrystallization. To a mixture of 77 grams of anhydrous caffeine (AMC Chemicals, Avenel, N.J.) and 500 grams of sucrose was added 150 grams of water. The mixture was heated to 255° F. and the syrup was transferred to the mixer and continually stirred. Peppermint oil (5.8 grams, U.S. Ingredients, Aurora, Ill.), and 10 drops of liquid blue food coloring are added. The mixture passes through a sieve mesh #60 and is compressed into 750 mg tablets. Each tablet provides 100 mg of caffeine and has a pleasant, sweet, mint character.

EXAMPLE 3

[0049] This example describes the creation of concentrated caffeine crystals, encapsulated with flavor and color, using cocrystallization. Sugar (200 grams), anhydrous caffeine (73.74 grams), and water (50 grams) are heated until 255° F., following the process detailed in Example One. Peppermint oil (2.76 grams, U.S. Ingredients, Aurora, Ill.)

and 10 drops liquid blue food coloring are added. A blend of 75 mg of the encapsulated drug and 675 mg of tableting sugar (Di-Pac®, Domino Sugar Corp., New York, N.Y.) are compressed into a tablet yielding 20 mg of caffeine.

EXAMPLE 4

[0050] This example describes the encapsulation of estradiol via cocrystallization. Five hundred grams of granulated sugar and 150 grams of water are heated to 255° F., following the process detailed in Example One. Estradiol (0.167 grams) is added to the mixture along with flavor (5.1 grams of peppermint oil, U.S. Ingredients, Aurora, Ill.) and color (10 drops of liquid blue food coloring, McCormick & Co., Hunt Valley, Md.). The mixture passes through a sieve mesh #60 and is compressed into 750 mg tablets. Each tablet provides 0.25 mg of estradiol for estrogen therapy and has a pleasant, sweet, mint character. Estrogens, such as estradiol, have been shown to be ten to twenty times more effective sublingually than orally (Miescher and Gasche, 1942).

EXAMPLE 5

[0051] This example describes the encapsulation of estradiol via extrusion, as described in U.S. Pat. No. 5,786,017. Saccharose (42.6%), maltodextrin (42.6%), estradiol (0.34%), water (3.96%), peppermint oil (10.0%), lecithin (0.5%), and FD&C Blue 1 (0.001%) are blended together. The powder is fed into a twin screw cooker extruder and heated to 150° C. The mixture is extruded, cooled, ground into rods, and screened. The resulting crystals, containing the drug, flavor, and color, are combined with tableting sugar (Di-Pac®, Domino Sugar Corp., New York, N.Y.). A blend of 75 mg of the encapsulated drug and 675 mg of the tableting sugar can be compressed into tablets that yield 0.25 mg estradiol.

EXAMPLE 6

[0052] This example describes the encapsulation of ibuprofen through cocrystallization. Five hundred grams of sucrose and 150 grams of water are heated to 255° F. Ibuprofen (126.58 grams) and peppermint oil (6.33 grams) are added while vigorously mixed. The resulting powder passes through a sieve mesh #60 and is compressed into 750 mg tablets. Each tablet provides 150 mg of ibuprofen.

[0053] Ibuprofen is a non-steroidal anti-inflammatory drug that reduces the level of prostaglandins in the body. Ibuprofen has been shown to be an effective treatment for fever, cold and flu, arthritis, gout, back aches, dental pain, head ache, migraine, muscle aches and pains, sinusitis.

[0054] Ibuprofen has a high lipid/oil partition coefficient, allowing it to be readily absorbed through the lipid membranes. Lower levels are required due to the rapid absorption through the oral mucosa. Encapsulation of the ibuprofen with flavor and sweetener masks the bitterness of the drug, allowing it to be palatable to the consumer.

EXAMPLE 7

[0055] This example describes the encapsulation of progesterone through cocrystallization. Five hundred grams of sucrose and 150 grams of water are heated to 255° F. Progesterone (126.58 grams) and peppermint oil (6.33 grams) are added while vigorously mixed. The resulting

powder passes through a sieve mesh #60 and is compressed into 750 mg tablets. Each tablet provides 150 mg of progesterone.

[0056] Postmenopausal estrogen replacement therapy is often prescribed, but current treatments suffer from poor patient compliance as many women object to some of the side-effects and the inconvenience of the pharmaceutical forms of the medication. Sublingual applications of progesterone have been shown to be 50% more effective than oral applications (Joel, 1942). By combining the hormone with flavor and sweetener, this invention provides a pleasant tasting and convenient delivery form for those on hormone replacement therapy.

EXAMPLE 8

[0057] This example describes the encapsulation of warfarin, an anticoagulant used for the prevention and treatment of blood clots and heart attacks, using cocrystallization. The procedure of Example One is repeated using 17.42 grams of sodium warfarin and 5.23 grams of peppermint oil (U.S. Ingredients, Aurora, Ill.). The resulting 750 mg tablet contains 25 mg of warfarin.

EXAMPLE 9

[0058] This example describes the encapsulation of nicotine using cocrystallization. The procedure of Example Three is repeated using 5.54 grams of nicotine and 2.08 grams of peppermint oil (U.S. Ingredients, Aurora, Ill.). A blend of 75 mg of the encapsulated drug and 675 mg of tableting sugar (Di-Pac®, Domino Sugar Corp., New York, N.Y.) are compressed into a tablet yielding 2 mg of nicotine. Nicotine passes through the oral mucosa with considerable ease and the tablet can be used to help patients stop smoking.

EXAMPLE 10

[0059] This example describes the encapsulation of diphenhydramine, an antihistamine and sedative, via spray drying. One hundred grams of diphenhydramine hydrochloride is combined with 500 grams of water and 200 grams of an enzymatically converted starch derivative, an example of which is described by U.S. Pat. No. 6,086,917. The mixture is heated to 60° C. until starch dissolution is complete and then lowered to 40° C. Peppermint oil (75 grams) is added and emulsified at high speed for approximately three minutes. The emulsion is then spray dried into a powder using standard techniques known to those who practice the art. The resulting powder is combined with tableting sugar (5%:95% w/w) and compressed into tablets with a lubricating agent, such as magnesium stearate. The resulting 750 mg tablet contains 10 mg of diphenhydramine.

EXAMPLE 11

[0060] This example describes the encapsulation of acetaminophen, a common pain reliever and fever reducer, using coated rotogranules. The rotogranulating and coating process is described in U.S. Pat. No. 5,460,825. Rotogranules are created by spraying water, at a rotor speed of 400-500 RPM, onto a mixture of 200 grams of acetaminophen, 7.5 grams of artificial grape oil, 18.75 grams of hydroxypropylmethyl cellulose, and 111.24 grams of sucrose. The granules are dried to 30-35° C., at a rotor speed of 250 RPM. The granules are coated using 37.5 grams of a

solution by weight of a 70:30 blend of cellulose acetate to hydroxypropyl cellulose. The coated granules are combined with 375 grams of compressible sugar and formed into 750 mg tablets yielding 200 mg of acetaminophen.

EXAMPLE 12

[0061] This example describes the encapsulation of phenmetrazine, an appetite suppressant, via cocrystallization. Phenmetrazine (9.70 grams) is added to 500 grams of sorbitol (70% solution, Archer Daniels Midland, Decatur, Ill.). The mixture is heated to 255° F. and the syrup is transferred to a mixer and continually stirred. Peppermint oil (3.63 grams, U.S. Ingredients, Aurora, Ill.), and 10 drops of liquid blue food coloring are added. The mixture passes through a sieve mesh #60 and is compressed into 750 mg tablets. Each tablet provides 20 mg of phenmetrazine.

EXAMPLE 13

[0062] This example describes the encapsulation of benzocaine using cocrystallization. Benzocaine is a reducing aid used by those controlling their diet. The procedure of Example Three is repeated using 17.58 grams of benzocaine and 2.20 grams of peppermint oil (U.S. Ingredients, Aurora, Ill.). A blend of 75 mg of the encapsulated drug and 675 mg of sorbitol (Archer Daniels Midland, Decatur, Ill.) are compressed into a tablet yielding 6 mg of benzocaine.

EXAMPLE 14

[0063] This example describes the encapsulation of phenylephrine hydrochloride via extrusion. Phenylephrine hydrochloride stimulates the sympathetic nervous system, lowers blood pressure, and constricts blood vessels. The encapsulation process detailed in Example Five is repeated using 36.0% saccharose, 36.0% maltodextrin, 0.13% of phenylephrine hydrochloride and 4.2% of water. A blend of 75 mg of the encapsulated drug and 675 mg of the tableting sugar (Di-Pac®) can be compressed into tablets that yield 10 mg phenylephrine hydrochloride.

EXAMPLE 15

[0064] This example describes the encapsulation of amobarbital, a barbiturate, through the process of cocrystallization. The process described in Example Two is repeated using 77 grams of amobarbital. Each 750 mg tablet provides 100 mg of amobarbital.

EXAMPLE 16

[0065] This example describes the encapsulation of phenylpropanolamine hydrochloride (PPA) using cocrystallization. PPA stimulates the sympathetic nervous system and a bronchodilator that is used as a nasal decongestant and dieting aid. The procedure of Example Eight is repeated using 17.42 grams of PPA and the resulting 750 mg tablet contains 25 mg of PPA.

EXAMPLE 17

[0066] This example describes the encapsulation of dimenhydrinate using cocrystallization. Dimenhydrinate is an antihistamine used to prevent nausea and vomiting associated with "morning" sickness in pregnant women and motion sickness. The procedure of Example Eight is

repeated using 17.42 grams of dimenhydrinate and the resulting 750 mg tablet contains 25 mg of dimenhydrinate.

EXAMPLE 18

[0067] This example describes the encapsulation of pseudoephedrine hydrochloride using cocrystallization. Pseudoephedrine hydrochloride is a vasoconstrictor and bronchodilator and is used as a nasal decongestant and for the treatment of allergies. The procedure of Example Eight is repeated using 17.42 grams of pseudoephedrine. The resulting 750 mg tablet contains 25 mg of pseudoephedrine.

EXAMPLE 19

[0068] This example describes the encapsulation of meclizine using cocrystallization. Meclizine is antihistamine and is used for the treatment of motion sickness. The procedure of Example Eight is repeated using 17.42 grams of meclizine. The resulting 750 mg tablet contains 25 mg of meclizine.

EXAMPLE 20

[0069] This example describes the encapsulation of phenobarbital sodium using cocrystallization. Phenobarbital sodium is a long acting sedative, hypnotic, and anticonvulsant. The procedure of Example Eight is repeated using 17.42 grams of phenobarbital sodium. The resulting 750 mg tablet contains 25 mg of phenobarbital sodium.

EXAMPLE 21

[0070] This example describes the encapsulation of testosterone using cocrystallization. Testosterone is a steroid and an anti-estrogenic hormone. The procedure of Example Eight is repeated using 17.42 grams of testosterone. The resulting 750 mg tablet contains 25 mg of testosterone.

EXAMPLE 22

[0071] This example describes the encapsulation of prednisolone using cocrystallization. Prednisolone is an immuno-suppressant and used for the treatment for severe inflammation. The procedure of Example Eight is repeated using 17.42 grams of prednisolone. The resulting 750 mg tablet contains 25 mg of prednisolone.

EXAMPLE 23

[0072] This example describes the encapsulation of prednisone using cocrystallization. Prednisone is an immuno-suppressant and used for the treatment for severe inflammation, acute attacks of multiple sclerosis, arthritis, and irritable bowel syndrome. The procedure of Example Eight is repeated using 17.42 grams of prednisone. The resulting 750 mg tablet contains 25 mg of prednisone.

EXAMPLE 24

[0073] This example describes the encapsulation of diazepam, a tranquilizer and skeletal muscle relaxant, using cocrystallization. The encapsulation procedure of Example Nine is repeated using 5.54 grams of diazepam, yielding a tablet with 2 mg of diazepam.

EXAMPLE 25

[0074] This example describes the encapsulation of dyclonine hydrochloride, an anesthetic that relieves minor sore

throat and mouth pain, using cocrystallization. The encapsulation procedure of Example Nine is repeated using 5.54 grams of dyclonine hydrochloride, which yields a tablet with 2 mg of dyclonine hydrochloride.

EXAMPLE 26

[0075] This example describes the encapsulation of chlorpheniramine using coacervation. Chlorpheniramine is an antihistamine used as a decongestant and treatment of allergy symptoms. A solution of 80 ml of ethanol and 5.0 grams of Castor Wax A (mp 85° C.) is boiled to 78° C. as detailed in U.S. Pat. No. 4,102,806. The mixture is transferred to a propeller mixer and 0.77 grams of chlorpheniramine and 1.44 grams of peppermint oil are added. The encapsulated drug and flavor are centrifuged to remove the ethanol and dried under reduced pressure and at 40° C. for three hours. The resulting powder is screened through a 60 mesh sieve. The resulting material is combined with tableting sugar (5%:95% w/w ratio) and compressed into 750 mg tablets, such that each tablet contains 4 mg of chlorpheniramine.

EXAMPLE 27

[0076] This example describes the encapsulation of cyclizine hydrochloride via cocrystallization. Cyclizine hydrochloride is an antihistamine used in the prevention and treatment of nausea, vomiting, and dizziness associated with motion sickness. 500 grams of sucrose and 150 grams of water are heated to 255° F. The syrup is transferred to the mixer and continually stirred. Peppermint oil (5.41 grams, U.S. Ingredients, Aurora, Ill.), cyclizine hydrochloride (36.10 grams), and 20 drops of liquid blue food coloring are added. The mixture passes through a sieve mesh #60 and is compressed into 750 mg tablets. Each tablet provides 50 mg of cyclizine hydrochloride.

EXAMPLE 28

[0077] This example describes the encapsulation of medicines for the treatment of a hangover, including a combination of pain reliever and stimulants. The medicines are encapsulated via cocrystallization. A mixture of 300 grams of sucrose and 100 grams of water is heated to 255° F. and transferred to a mixer. The following components are added slowly while vigorously mixing: 122.30 gram of aspirin (Rhodia, Cranbury, N.J.), 30.58 grams of anhydrous caffeine (AMC Chemicals, Avenel, N.J.), 5.73 grams of peppermint oil (U.S. Ingredients, Aurora, Ill.), and 20 drops of blue food coloring (McCormick & Co., Hunt Valley, Md.). The resulting powder is compressed into tablets, each providing 200 mg aspirin and 50 mg of caffeine, for fast acting relief of a headache or hangover.

[0078] While the invention has been described with reference to specific examples and processes, these were for purposes of illustration only and should not be construed to limit the scope of the present invention.

What is claimed is:

1. A dry particulate drug delivery system for dissolution of pharmaceutical compounds in the mouth, comprising:

a therapeutically-effective amount of at least one drug, and an encapsulant, wherein said at least one drug is encapsulated by said encapsulant.

2. The dry particulate drug delivery system of claim 1, further comprising at least one volatile flavorant.

3. The dry particulate drug delivery system of claim 1, further comprising at least one sweetener.

4. The dry particulate drug delivery system of claim 3, further comprising at least one volatile flavorant.

5. The dry particulate drug delivery system of claim 1, wherein said encapsulant is a sucrose-based matrix.

6. The dry particulate drug delivery system of claim 1, wherein said therapeutically effective amount of said at least one drug is dependent on the desired dosage, method of encapsulation, absorption characteristics, and desired tablet size.

7. The dry particulate drug delivery system of claim 1, wherein said drug is a therapeutic agent selected from the group consisting essentially of anesthetics, decongestants, antihistamines, antitussives, antibiotics, analgesics, alkaloids, amphetamines, hormones, barbiturates, analeptics and mixtures thereof.

8. The dry particulate drug delivery system of claim 7, wherein said alkaloids are selected from the group consisting essentially of morphine, codeine, caffeine, and cocaine.

9. The dry particulate drug delivery system of claim 7, wherein said hormones are selected from the group consisting essentially of adrenaline and epinephrine.

10. The dry particulate drug delivery system of claim 3, wherein said at least one sweetener is selected from the group consisting essentially of sucrose, fructose, dextrose, lactose, mannitol, sorbitol, maltose, xylitol, saccharin and saccharin sodium, cyclamates, neotame, aspartame, sucralose, acesulfame potassium and mixtures thereof.

11. The dry particulate drug delivery system of claim 1, further comprising at least one of natural and artificial sweeteners, colors, preservatives, fillers, binders, lubricants, suspending agents, acids, buffers, and stabilizing agents.

12. The dry particulate drug delivery system of claim 1, wherein said system is a compressed tablet.

13. The dry particulate drug delivery system of claim 1, wherein said system is a chewing gum.

14. The dry particulate drug delivery system of claim 1, wherein said drug is encapsulated by a method selected from the group consisting essentially of spray drying, air suspension coating, extrusion, spray cooling and chilling, emulsion, microemulsion, adsorption, centrifugal extrusion, rotational suspension separation, rotoagranulation, coacervation, continuous crystallization, cocrystallization, inclusion, and liposome formation.

15. The dry particulate drug delivery system of claim 14, wherein aspirin is encapsulated by said cocrystallization method.

16. The dry particulate drug delivery system of claim 14, wherein caffeine is encapsulated by said cocrystallization method.

17. The dry particulate drug delivery system of claim 14, wherein estradiol is encapsulated by said cocrystallization method.

18. The dry particulate drug delivery system of claim 14, wherein estradiol is encapsulated by said extrusion method.

19. The dry particulate drug delivery system of claim 14, wherein ibuprofen is encapsulated by said cocrystallization method.

20. The dry particulate drug delivery system of claim 14, wherein progesterone is encapsulated by said cocrystallization method.

21. The dry particulate drug delivery system of claim 14, wherein warfarin is encapsulated by said cocrystallization method.

22. The dry particulate drug delivery system of claim 14, wherein nicotine is encapsulated by said cocrystallization method.

23. The dry particulate drug delivery system of claim 14, wherein diphenhydramine is encapsulated by said spray drying method.

24. The dry particulate drug delivery system of claim 14, wherein acetaminophen is encapsulated by said roto granulating method.

25. The dry particulate drug delivery system of claim 14, wherein phenmetrazine is encapsulated by said cocrystallization method.

26. The dry particulate drug delivery system of claim 14, wherein benzocaine is encapsulated by said cocrystallization method.

27. The dry particulate drug delivery system of claim 14, wherein phenylephrine hydrochloride is encapsulated by said cocrystallization method.

28. The dry particulate drug delivery system of claim 14, wherein amobarbital is encapsulated by said cocrystallization method.

29. The dry particulate drug delivery system of claim 14, wherein phenylpropanolamine hydrochloride is encapsulated by said cocrystallization method.

30. The dry particulate drug delivery system of claim 14, wherein dimenhydrinate is encapsulated by said cocrystallization method.

31. The dry particulate drug delivery system of claim 14, wherein pseudoephedrine hydrochloride is encapsulated by said cocrystallization method.

32. The dry particulate drug delivery system of claim 14, wherein meclizine is encapsulated by said cocrystallization method.

33. The dry particulate drug delivery system of claim 14, wherein Phenobarbital sodium is encapsulated by said cocrystallization method.

34. The dry particulate drug delivery system of claim 14, wherein testosterone is encapsulated by said cocrystallization method.

35. The dry particulate drug delivery system of claim 14, wherein prednisolone is encapsulated by said cocrystallization method.

36. The dry particulate drug delivery system of claim 14, wherein diazepam is encapsulated by said cocrystallization method.

37. The dry particulate drug delivery system of claim 14, wherein dyclonine hydrochloride is encapsulated by said cocrystallization method.

38. The dry particulate drug delivery system of claim 14, wherein chlorpheniramine is encapsulated by said coacervation method.

39. The dry particulate drug delivery system of claim 14, wherein cyclizine hydrochloride is encapsulated by said cocrystallization method.

40. The method of dissolving a pharmaceutical compound in the mouth of a user, comprising the steps of:

encapsulating a therapeutically-effective amount of at least one drug within an encapsulant and forming an encapsulated drug,

inserting said encapsulated drug into the mouth of the user,

subjecting said encapsulated drug to fluids secreted within the mouth of said user,

dissolving said encapsulant and releasing said drug in said mouth,

dissolving said drug within said mouth of said user.

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(75) **Inventors:** **Matthew F. Heil, Duluth, GA**
(US); Glynn Wilson, Duluth, GA
(US)

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Correspondence Address:

PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE, SUITE 1200, 1201
PEACHTREE STREET
ATLANTA, GA 30361

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(73) **Assignee:** **Auriga Laboratories, Inc.**

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(57) **ABSTRACT**

A mixed-release tablet or capsule formulation including vehicles for the delivery of a plurality of drugs in various combinations of immediate release, extended release, and/or delayed release modes over a predetermined time period have been developed, which provide for controlled release not just of the drugs, but controlled release that is designed to create more effective coordination between the drugs being delivered. The drugs can be any medically and/or physiologically appropriate combination of drugs and active ingredients, preferably decongestant drugs, antihistamines, expectorants, antitussives, cough suppressants, and drying agents.

Related U.S. Application Data

(60) **Provisional application No. 60/752,057, filed on Dec. 21, 2005, provisional application No. 60/761,766, filed on Jan. 25, 2006, provisional application No. 60/791,408, filed on Apr. 13, 2006.**

SEQUENTIAL RELEASE PHARMACEUTICAL FORMULATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] Priority is claimed to U.S. application Nos. 60/752,057, filed Dec. 21, 2005; 60/761,766 filed Jan. 25, 2006; and 60/791,408 filed Apr. 13, 2006

FIELD OF THE INVENTION

[0002] The present invention provides a mixed-release formulation that contains a plurality of active therapeutic agents and provides continuous immediate and/or extended dosing and delayed dosing for a predetermined time period, up to at least 12 hours.

BACKGROUND OF THE INVENTION

[0003] Existing methods for the treatment of a variety of conditions involve the administration of more than one active agent using formulations that allow for immediate as well as controlled release. The drug delivery profiles of such formulations are simple, usually involving the immediate release of an active ingredient, followed by the sustained release of the same ingredient, or a different active ingredient, delayed for a certain period of time. However, many of these formulations fail to take advantage of combining multiple controlled, delayed, or immediate release profiles within a single preparation other than just combinations of immediate and delayed release. In particular, present methods for the treatment of cold or allergic rhinitis symptoms rely upon a wide variety of agents, most principally antihistamines (e.g., Chlorpheniramine), expectorants (e.g., guaifenesin), decongestants (e.g., pseudoephedrine or phenylephrine) and drying agents (e.g., the antisecretory drug methscopolamine). Dextromethorphan is antitussive agent used in many over-the-counter cold medications. It has an opioid-like structure but, being a D-isomer, it does not possess the analgesic or addictiveness of opioids. It acts centrally to relieve cough, similar to opioids. It is active against dry cough and does not exhibit significant expectorant properties for productive cough. Methscopolamine nitrate is an anticholinergic and is a derivative of scopolamine. It possess the peripheral actions of the belladonna alkaloids, but does not exhibit the central actions because of its inability to cross the blood-brain barrier. In cough-cold preparations, it is most often used for its anti-secretory effect on the upper respiratory system. However, methscopolamine has a relatively short plasma half-life and needs an extended release formulation to provide symptomatic relief over extended periods of time. Chlorpheniramine, often administered as the maleate salt, is a short-acting antihistamine (H₁) compound that also has a short plasma half-life. Chlorpheniramine also requires an extended release formulation to provide extended symptomatic relief in cough-cold formulations. Phenylephrine is an alpha agonist that acts as a decongestant in cough-cold formulations. Phenylephrine also requires a longer acting formulation. Phenylephrine hydrochloride, also known as (S)-3-hydroxy-[alpha]-(methylamino) methylbenzene methanol hydrochloride, is an orally effective nasal decongestant. Phenylephrine is a synthetic, optically active sympathomimetic amine that has one hydroxyl group on the benzene ring. The hydroxyl group is

meta to the aliphatic side chain. The meta position affords optimal activity. Phenylephrine (neo-synephrine) replaced an older preparation, synephrine, in which the hydroxyl was in the para position. Phenylephrine hydrochloride is available in the form of the levorotatory isomer, which is a white, odorless, non-hygroscopic, crystalline compound possessing a bitter taste. Phenylephrine hydrochloride has a melting point of 140-145° C. and is freely soluble in water and alcohol. Decongestant compounds in the form of their free bases as well as their pharmaceutically acceptable salts, e.g., hydrochloride, citrate, maleate, tannate, etc., are used. Expectorants, such as guaifenesin, change a dry, unproductive cough to one that is more productive and less frequent. Guaifenesin, known chemically as 3-(2-methoxyphenoxy)-1,2-propanediol, is a crystalline powder, which is soluble in water and alcohol. It is indicated in the USP Drug information as an expectorant for the symptomatic relief of cough due to colds and minor upper respiratory infections.

[0004] Phenylephrine may be present in amounts of between about 15 and about 60 milligrams per capsule, preferably from about 5 milligrams to about 30 milligrams per capsule, with half or less of that amount used in a pediatric form of the formulation. Delsym DM® (Novartis) is an example of a sustained-release dextromethorphan composition. The sustained-release characteristics of the composition are achieved by the use of small particles of an ion-exchange resin bound to the dextromethorphan that delay release of the drug in the gastrointestinal tract. However, the bioavailability of dextromethorphan is relatively low due to the strong bond between residual amounts of dextromethorphan and the ion exchange resin. The total percentage of dextromethorphan released from dextromethorphan-ion exchange resin complexes is incomplete, and under certain in vitro conditions it has been observed that even after a twelve hour period of time, about 20% of dextromethorphan remains bound to the ion exchange resin.

[0005] Examples of the preparation of sustained release formulations of individual cough-cold medicines include U.S. Pat. No. 6,416,786 to Mulay (sustained release formulation of guaifenesin); U.S. Patent Application Publication No. 20050152967 by Tengler et al. (mixed release formulations of an expectorant for immediate release and a decongestant for extended release); U.S. Pat. No. 6,955,821 to Davis et al. (sustained release formulation of guaifenesin and at least one other drug, wherein guaifenesin is formulated for both immediate and extended release); and U.S. Pat. No. 6,372,252 Blume et al. (sustained release guaifenesin formulations where guaifenesin is formulated for both immediate and extended release).

[0006] While some mixed release compositions have been described, as discussed above, there is still a need in the art to create controlled release pharmaceutical formulations with better sequential release characteristics that orchestrate the symphony of symptomatic release agents to better fit the needs of patients suffering from a cold, or those experiencing cold like symptoms in terms of decongestant, expectorant and drowsiness characteristics.

[0007] Therefore it is an object of the present invention to provide a formulation with a tighter control of different drug release than what is achieved with an immediate release-sustained release formulation.

[0008] It is a further object of the invention to provide a formulation including an expectorant for immediate and extended release, and a cough suppressant for delayed and

28

extended release, wherein the release profiles of the ingredients are orchestrated to better co-ordinate the production and clearance of mucus and cough suppression.

SUMMARY OF THE INVENTION

[0009] A mixed-release tablet or capsule formulation including vehicles for the delivery of a plurality of drugs in various combinations of immediate release, extended release, and/or delayed release modes over a predetermined time period have been developed which provide for controlled release not only of the drugs, but controlled release that is designed to create more effective coordination between the drugs being delivered. The drugs can be any medically and/or physiologically appropriate combination of active agents and active ingredients, preferably decongestants, antihistamines, expectorants, antitussives, cough suppressants, and drying agents. Representative decongestants include phenylephrine (bitartrate, tannate, HBr, or HCl salts), phenylpropanolamine (HCl), pseudoephedrine (HCl), and combinations thereof. Representative antihistamines include chlorpheniramine (maleate), brompheniramine (maleate), dexchlorpheniramine (maleate), dexbrompheniramine (maleate), triprolidine (HCl), diphenhydramine (HCl), doxylamine (succinate), triproclennamine (HCl), cyproheptadine (HCl), bromodiphenhydramine (HCl), phenindamine (tartrate), pyrilamine (maleate, tartrate), azatadine (maleate), and combinations thereof. Representative expectorants include guaifenesin, terpin hydrate, (glyceryl guaiacolate), potassium (iodide, citrate), potassium guaiacolsulfonate, and combinations thereof. Representative antitussive agents include caraminphen (edisylate), dextromethorphan (HBr), codeine (phosphate, sulfate), hydrocodone (bitartrate), and combinations thereof.

[0010] Appropriate vehicles for the delivery of the drugs may be liquid, gel, semisolid, paste, or solid. More specifically, these vehicles may be microparticles, for example, microspheres or other micronized forms, granules, beads, or resins. In various embodiments, the tablet or capsule pharmaceutical formulation includes one or more of the following granules: immediate-release granules, delayed release granules, extended release granules; and optionally free drug or a plurality of different drugs, wherein each formulation of granules include individual beads containing soluble and/or insoluble polymers and an active drug or a plurality of drugs. In another embodiment, the formulations include a decongestant for immediate and extended release, an antihistamine for extended release, and a drying agent for delayed and extended release, wherein the release profiles of the ingredients are controlled to orchestrate the effectiveness of their pharmacological action. For example, the formulation may comprise an expectorant for immediate and extended release, wherein over 90% of the drug is released substantially linearly over a 12 hour period of time, and a cough suppressant for delayed and extended release, wherein over 90% of the drug is released between 4 to 12 hours, wherein the release profiles of the ingredients are orchestrated to co-ordinate the production and clearance of mucus and cough suppression. In one embodiment, the pharmaceutical composition includes an extended release expectorant active drug packaged for extended release of over 90% of the expectorant active drug released substantially linearly over up to at least a 12 hour period of time; and an antitussive active drug packaged for immediate and sustained release,

such that up to 50% of the antitussive active drug is released in immediate fashion over the first 1 to 4 hours, followed by sustained release of the antitussive drug, such that up to 100% of the antitussive active drug is released between 4 to 12 hours. In another embodiment, the pharmaceutical formulations include an expectorant for immediate and extended release, and a cough suppressant for delayed and extended release, wherein the release profiles of the ingredients are orchestrated to better co-ordinate the production and clearance of mucus and cough suppression.

[0011] The pharmaceutical formulation may include a combination of the anti-tussive, anti-histamine and drying agent; a combination of the decongestant and drying agent; a combination of the decongestant and cough suppressant; a combination of the expectorant and cough suppressant; or a combination of the expectorant and anti-tussive in a capsule, tablet, oral rapid dissolving tablet, softgel, gelcap, film, gum, pastille, lozenge, disk, or wafer form. The antitussives, antihistamines, decongestants, expectorants, drying agents or combinations thereof may be formulated as immediate-release granules, delayed release granules, extended release granules; or optionally as a free drug depending on the desired pharmacological effect. The formulations may include effective amounts of each of dextromethorphan (HBr), chlorpheniramine (maleate), methscopolamine (nitrate), pseudoephedrine (HCl), phenylephrine (HCl), guaifenesin, and hydrocodone (bitartrate). The anti-tussive active drug can be dextromethorphan in a form such as a sustained release granule, a sustained release matrix, or combinations thereof; and the anti-histamine active drug can be chlorpheniramine in a form such as a sustained release bead, a sustained release matrix, or combinations thereof. The drying agent active drug can be methscopolamine in the form of a delayed release granule. The decongestant can be pseudoephedrine in the form of a mixture of an immediate release bead, an immediate release matrix, and a sustained release bead, a sustained release matrix, or combinations thereof.

[0012] In one embodiment, the tablet or capsule pharmaceutical formulation can include:

[0013] (a) an anti-tussive active drug within a granule matrix packaged for extended release of over 90% of the active drug released substantially linearly over up to at least a 12 hour period of time;

[0014] (b) an anti-histamine active drug packaged for extended release of over 90% of the active drug released substantially linearly over up to at least a 12 hour period of time; and

[0015] (c) a drying agent active drug packaged for delayed and extended release of over 90% of the active drug released substantially linearly over a period of 8 hours following an initial delay of release of from about 2 to about 4 hours.

[0016] In another embodiment, the pharmaceutical composition can include:

[0017] (a) an immediate release decongestant active drug packaged immediate release of over 60-80% of the active drug within from about 90 minutes to about 120 minutes following dosing;

[0018] (b) an extended release decongestant active drug packaged for extended release of over 90% of the active drug released substantially linearly over up to a 12 hour period of time; and

- [0019] (c) a drying agent active drug packaged for delayed and extended release of over 90% of the active drug released substantially linearly over up to at least an 8 hour period following an initial delay of release of from about 2 to about 4 hours.
- [0020] In another embodiment, the pharmaceutical composition can include:
- [0021] (a) an immediate release expectorant active drug packaged for immediate release of over 60-80% of the active drug within from about 90 minutes to about 120 minutes following dosing;
- [0022] (b) an extended release expectorant active drug packaged for extended release of over 90% of the active drug released substantially linearly over up to at least a 12 hour period of time;
- [0023] (c) optionally, a drying agent active drug package for delayed and extended release of over 90% of the active drug released substantially linearly over up to at least an 8 hour period following an initial delay of release of from about 2 to about 4 hours; and
- [0024] (d) optionally, a cough suppressant active drug packaged for delayed and extended release of over 90% of the active drug released substantially linearly over up to at least an 8 hour period following an initial delay of release of from about 2 to about 4 hours.
- [0025] In another embodiment, pharmaceutical composition can include:
- [0026] (a) an immediate release expectorant active drug packaged for immediate release of over 60-80% of the active drug within from about 90 minutes to about 120 minutes following dosing;
- [0027] (b) an extended release expectorant active drug packaged for extended release of over 90% of the active drug released substantially linearly over up to at least a 12 hour period of time;
- [0028] (c) optionally, a drying agent active drug packaged for delayed and extended release of over 90% of the active drug released substantially linearly over up to at least an 8 hour period following an initial delay of release of from about 2 to about 4 hours; and
- [0029] (d) optionally, an antitussive active drug packaged for delayed and extended release of over 90% of the active drug released substantially linearly over up to at least an 8 hour period following an initial delay of release of from about 2 to about 4 hours.
- [0030] In variations of these embodiments, the immediate release forms of the drugs are optional.
- [0031] In a specific embodiment, the pharmaceutical composition can include:
- [0032] (a) an extended release form of guaifenesin packaged for extended release of over 90% of the active drug released substantially linearly over up to at least a 12 hour period of time;
- [0033] (c) hydrocodone formulated for delayed and extended release of over 90% of the active drug released substantially linearly over up to at least an 8 hour period following an initial delay of release of from about 2 to about 4 hours.
- [0034] A method for providing a sequential-release formulation has also been developed, wherein different types of granules are loaded into a capsule, wherein each type of granule includes individually an extended release anti-tussive, an extended release antihistamine and a drying agent in a delayed release form, and wherein the capsule further

includes one or more excipients. Alternatively, a sequential-release tablet formulation is made by compressing a mixture of excipients and a mixture of granules into a tablet, wherein each type of granule includes individually an extended release anti-tussive, an extended release anti-histamine and a drying agent in a delayed release form. The mixture of excipients may further include free active drug. The anti-tussive agent can be dextromethorphan, the anti-histamine can be chlorpheniramine, and the drying agent can be methscopolamine.

[0035] Another method for making a sequential-release formulation includes loading a mixture of different types of granules and an excipient formulation into a capsule, wherein the mixture of granules includes an active drug within a polymer matrix and wherein the active drug mixture includes an immediate release decongestant, an extended release decongestant, and a drying agent in a delayed and extended release form. The anti-tussive agent can be dextromethorphan, the anti-histamine can be chlorpheniramine, and the drying agent can be methscopolamine.

[0036] Still another method for making a sequential-release formulation includes loading a mixture of different types of granules into a capsule, wherein each type of granule includes individually an extended release expectorant, and a cough suppressant in a delayed and extended release form, and wherein the capsule includes one or more excipients.

[0037] In one embodiment, the expectorant can be guaifenesin and the cough suppressant can be hydrocodone. In one embodiment of a formulation of hydrocodone and guaifenesin, up to 20% of the hydrocodone can be released in a sustained fashion over the first 1 to 4 hours, followed by the sustained release of up to 100% of the remaining amount of the hydrocodone between 4 to 12 hours.

[0038] In another formulation of hydrocodone and guaifenesin, the release of hydrocodone is achieved in two sequential immediate release pulses, where between 0 to 5 mg of hydrocodone is released between 1 to 4 hours, and 5 to 10 mg of the hydrocodone is released after 4 to 6 hours. In yet another formulation of hydrocodone and guaifenesin, 20-35% of guaifenesin is released between 0 to 2 hours, 35-65% is released between 2 to 4 hours, and 65-90% is released between 4 to 8 hours. In another formulation of hydrocodone and guaifenesin, up to 50% of the hydrocodone (0-5 mg) is released between 1 to 4 hours, and 5 to 10 mg of the hydrocodone is released in a sustained fashion between 4 to 12 hours. In this specific formulation guaifenesin is released in a sustained fashion between 1-12 hours.

DETAILED DESCRIPTION OF THE INVENTION

[0039] Definitions

[0040] As used herein, "solid pharmaceutical compositions" include, but are not limited to, oral dosage forms such as tablets, capsules, caplets, gels, wafers, films, gums, pastilles, lozenges, matrices, disks. Such compositions are predominantly solid such that appropriate dosages are achieved by the subject without the need for a separate measuring device, such as a spoon, measuring cup or dropper. Such compositions can include liquid constituents or compositions, including gels and slurries.

[0041] As used herein "delayed release" means that about 90% or more of the active therapeutic agent administered

and contained within the formulation, for example within granules, is delayed for about 1 to 4 hours, more precisely, 2 to 4 hours, after administration, from being released from the granules and available to systemic exposure.

[0042] As used herein "sustained release" or "extended release" means that about 90% or more of the active therapeutic agent administered and contained within the formulation, for example, within granules, is released from the granules and available to systemic exposure over there period of time where release is sustained and released over a substantially linear rate.

[0043] As used herein "immediate release" means that at about 90% or more of the active therapeutic agent administered and contained within the formulation, for example, within granules, is release within a period of 1 to 3 hours after administration and available to systemic exposure. Immediate release may also be defined functionally as the release of over about 80 to 90 percent 15 (%) of the active ingredient within about 60, 90, 100 or 120 minutes or less.

[0044] As used herein, a "pulse" relates to a release of the active therapeutic agent at a contemplated point in time. For example, a pulse can be delayed, but once the point in time is reached following administration, the active therapeutic agent can be released immediately. Pulses can be sequential. For example, a first immediate release pulse can occur at time point X, which is followed later by a second immediate release pulse at time point Y. Although commencement of the second immediate release pulse is delayed in comparison to the commencement and possibly the completion of first time pulse, the release of the second will be immediate following the delay.

[0045] The term "about" in the context of numerical values and ranges refers to values or ranges that approximate or are close to the recited values or ranges such that the method or composition can perform as intended, as is apparent from the teachings contained herein. Thus, this term encompasses values beyond those simply resulting from systematic error. Typically, the term "about" means plus or minus ten percent.

I. Formulation

[0046] The formulations are based on the recognition that patients and physicians are looking to simplify the number of doses that a patient takes and to improve the timing of onset of drug action consistent with improving patient compliance and outcomes. The underlying rationale is the use of combinations of drugs in a single therapeutic preparation, where each active agent or drug, or groups of drugs is formulated in a specific release profile so as to provide in combination with the other actives agents to provide a sequence of complementary therapeutic actions. The therapeutic utility of the formulation is a result of orchestrating the overall utility of the therapeutic preparation over time. For example, a therapeutic formulation that is formulated to be taken in the early evening provides an immediate dose of guaifenesin that can assist in breaking up mucus and initiating a productive cough. As the guaifenesin action decreases, the drying and decongestant activities of a selectively delayed and controlled release methscopolamine and phenylephrine provides longer term drying and decongestant activity and which is less likely to interfere with the user's sleep.

[0047] Methscopolamine and phenylephrine can delayed for about 2-4 hours after administration and only released so as to provide a sequence of mucolytic and then decongestant

and drying effects better fitted with the patient's needs. Patients who have experienced an exposure to an allergen benefit from a rapid release of the antihistamine chlorpheniramine but, once removed from the presence the allergen, better benefit from the sustained release of a decongestant combined with the longer term drying effects of methscopolamine, the gradual controlled release of which is delayed 2-4 hours after dosing. By this time, the immediately released chlorpheniramine effects are declining and are supplemented by a sustained drying effect provided by methscopolamine and a decongestant effect provided by phenylephrine. This example also illustrates ways in which the combination of delayed, controlled and immediate release actives can be blended to avoid side effects found in some combinations of less skillfully regulated blends of actives. Chlorpheniramine and methscopolamine are highly effective in their own regard. For example, while both chlorpheniramine and methscopolamine are highly effective, both have anticholinergic activity which, when combined as in a simple controlled release preparation containing both actives, causes excessive and uncomfortable drying in some patients. However, by combining a release profile for chlorpheniramine that sequentially provides relief from the different actives, a therapeutic is created that is more effective in addressing both the short term and long term therapeutic needs of patients while avoiding unpleasant side effects resulting from less precise delivery profiles.

[0048] A. Pharmaceutically Active Compounds

[0049] The drugs may be any medically and/or physiologically appropriate combination of drugs and active ingredients described in United States Pharmacopoeia ("USP"), the Physician's Desk Reference ("PDR"), and the Food and Drug Administration ("FDA") publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," also known as the "Orange Book." The drugs can be any medically and/or physiologically appropriate combination of drugs and active ingredients, preferably decongestant drugs, antihistamines, expectorants, antitussives, cough suppressants, and drying agents. Representative decongestant active drugs include phenylephrine (bitartrate, tannate, HBr, HCl), phenylpropanolamine (HCl), pseudoephedrine (HCl), and combinations thereof. Representative antihistamine active drug include chlorpheniramine (maleate), brompheniramine (maleate), dexchlorpheniramine (maleate), dexbrompheniramine (maleate), triprolidine (HCl), diphenhydramine (HCl), doxylamine (succinate) n-pseudoephedrine (HCl), cyproheptadine (HCl), bromodiphenhydramine (HCl), phenindamine (tartrate), pyrilamine (maleate, tamate), azatadine (maleate), and combinations thereof. Representative expectorant active drug include guaifenesin, terpin hydrate, (glyceryl guaiacolate), potassium (iodide, citrate), potassium guaiacolsulfonate, and combinations thereof. Representative antitussive active drug include ephedrine (edisylate), dextromethorphan (HBr), codeine (phosphate, sulfate), hydrocodone (bitartrate), and combinations thereof. Representative cough suppressants include benzonatate, bromodiphenhydramine, brompheniramine, buclizine, carbinoxamine, chlorpheniramine, clemastine, codeine, cyclizine, dexchlorpheniramine, dextromethorphan, dihydrocodeine, diphenhydramine, diphenhydramine, doxylamine, homatropine, hydrocodone, meclizine, pheniramine, phenyltoloxamine, pyrilamine, trimethobenzamide, triprolidine. Representative drying agents include methscopolamine, scopolamine, meclizine, trimethobenzamide, dimen-

[0062] Surfactants may be anionic, cationic, amphoteric or nonionic active agents. Suitable anionic surfactants include, but are not limited to, those containing carboxylate, sulfate and sulfonate ions. Examples of anionic surfactants include sodium, potassium, ammonium or long chain alkyl ammonium salts of alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate; dialkyl sodium sulfo succinates, such as sodium dodecylbenzene sulfonate; dialkyl sodium sulfosuccinates, such as sodium bis-(2-ethylhexyloxy)-sulfonate; and alkyl sulfates such as sodium lauryl sulfate. Cationic surfactants include, but are not limited to quaternary ammonium compounds such as benzalkonium chloride, benzethonium chloride, cetrimonium bromide, stearyl dimethyl benzyl ammonium chloride, polyoxyethylene cocoamine. Examples of nonionic surfactants include ethylene glycol monostearate, propylene glycol monostearate, glyceryl monostearate, glyceryl stearate, sorbitan monooleate, sucrose acylate, PEG-150, PEG-400, PEG-400 monolaurate, polyoxyethylene monolaurate, polyoxyethylene octylphenyl ether.

nylether, PEG-1000 cetyl ether, polyoxyethylene tridecyl ether, polypropylene glycol butyl ether, Poloxamer® 401, stearyl monoisopropanolamide, and polyoxyethylene hydrogenated tallow amide. Examples of amphoteric surfactants include sodium N-dodecyl- β -alanine, sodium N-lauryl- β -iminodipropionate, myristoamphoacetate, lauryl betaine and lauryl sulfobetaine.

[0063] If desired, the tablets, beads granules or particles may also contain minor amount of nontoxic auxiliary substances such as wetting or emulsifying agents, dyes, pH buffering agents, and preservatives.

Extended Release Dosage Forms

[0064] The extended release formulations are generally prepared as diffusion or osmotic systems, for example, as described in "Remington—The science and practice of pharmacy" (20th ed., Lippincott Williams & Wilkins, Baltimore, Md., 2000). A diffusion system typically consists of two types of devices, reservoir and matrix, and is well known and described in the art. The matrix devices are generally prepared by compressing the drug with a slowly dissolving polymer carrier into a tablet form. The three major types of materials used in the preparation of matrix devices are insoluble plastics, hydrophilic polymers, and fatty compounds. Plastic matrices include, but not limited to, methyl acrylate-methyl methacrylate, polyvinyl chloride, and polyethylene. Hydrophilic polymers include, but are not limited to, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and Carbowax® 934, polyethylene oxides. Fatty compounds include, but are not limited to, various waxes such as a carnauba wax and glyceryl tristearate.

[0065] Alternatively, extended release formulations can be prepared using osmotic systems or by applying a semi-permeable coating to the dosage form. In the latter case, the desired drug release profile can be achieved by combining low permeable and high permeable coating materials in suitable proportion.

[0066] Extended release tablets containing hydrophilic polymers are prepared by techniques commonly known in the art such as direct compression, wet granulation, or dry granulation processes. Their formulations usually incorporate polymers, diluents, binders, and lubricants as well as the active pharmaceutical ingredient. The usual diluents include inert powdered substances such as any of many different kinds of starch, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders include substances such as starch, gelatin and sugars such as lactose, fructose, and glucose. Natural and synthetic gums, including acacia, alginates, methylcellulose, and polyvinylpyrrolidone can also be used. Polyethylene glycol, hydrophilic polymers, ethylcellulose and waxes can also serve as binders. A lubricant is necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

[0067] Extended release tablets containing wax materials are generally prepared using methods known in the art such as a direct blend method, a congealing method, and an aqueous dispersion method. In a congealing method, the drug is mixed with a wax material and either spray-congealed or congealed and screened and processed.

Delayed Release Dosage Forms

[0068] Delayed release formulations are created by coating a solid dosage form with a film of polymer which is insoluble in the acid environment of the stomach, and soluble in the neutral environment of small intestines.

[0069] The delayed release dosage units can be prepared, for example, by coating a drug or a drug-containing composition with a selected coating material. The drug-containing composition may be, e.g., a tablet for incorporation into a capsule, a tablet for use as an inner core in a "coated core" dosage form, or a plurality of drug-containing beads, particles or granules, for incorporation into either a tablet or capsule. Preferred coating materials include bioerodible, gradually hydrolyzable, gradually water-soluble, and/or enzymatically degradable polymers, and may be conventional "enteric" polymers. Enteric polymers, as will be appreciated by those skilled in the art, become soluble in the higher pH environment of the lower gastrointestinal tract or slowly erode as the dosage form passes through the gastrointestinal tract, while enzymatically degradable polymers are degraded by bacterial enzymes present in the lower gastrointestinal tract, particularly in the colon. Suitable coating materials for effecting delayed release include, but are not limited to, cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl methyl cellulose acetate succinate, hydroxypropylmethyl cellulose phthalate, methylcellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate, and other methacrylic resins that are commercially available under the tradename Eudragit® (Rohm Pharma, Westerstadt, Germany), including Eudragit® L30D-55 and L100-55 (soluble at pH 5.5 and above), Eudragit® L-100 (soluble at pH 6.0 and above), Eudragit® S (soluble at pH 7.0 and above, as a result of a higher degree of esterification), and Eudragits® NE, RL and PL of water-insoluble polymers having different degrees of permeability and expandability); vinyl polymers and copolymers such as polyvinyl pyrrolidone, vinyl acetate, vinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylacrylate-methyl acrylate copolymer; enzymatically degradable polymers such as azo polymers, pectin, chitosan, amylose and gum arabic; zein and shellac. Combinations of different coating materials may also be used. Multi-layer coatings using different polymers may also be applied.

[0070] The preferred coating weights for particular coating materials may be readily determined by those skilled in the art of evaluating individual release profiles for tablets, beads and granules prepared with different quantities of various coating materials. It is the combination of materials, method and technique of application that produce the desired release characteristics, which one can determine only from the clinical studies.

[0071] The coating composition may include conventional additives, such as plasticizers, pigments, colorants, stabilizing agents, glidants, etc. A plasticizer is normally present to reduce the fragility of the coating, and will generally represent about 10 wt. % to 50 wt. % relative to the dry weight of the polymer. Examples of typical plasticizer include polyethylene glycol, propylene glycol, triacetin, dimethyl phthalate, diethyl phthalate, dibutyl phthalate, dibutyl sebacate, triethyl citrate, tributyl citrate, triethyl acetyl citrate, castor oil and acetylated monoglycerides. A stabilizing agent is preferably used to stabilize particles in the dispersion. Typical stabilizing agents are nonionic emulsifiers, such as sorbitan esters, polysorbates and polyvinylpyrrolidone. Glidants are recommended to reduce sticking effects during film formation and drying, and will generally represent approximately 25 wt. % to 100 wt. % of the polymer weight in the coating solution. One effective glidant is talc. Other glidants such as magnesium stearate and glycerol monostearates may also be used. Pigments such as titanium dioxide may also be used. Small quantities of an anti-foaming agent, such as a silicone (e.g., simethicone), may also be added to the coating composition.

[0072] As will be appreciated by those skilled in the art and as described in the pertinent texts and literature, a number of methods are available for preparing drug-containing tablets, beads, granules or particles that provide a variety of drug release profiles. Such methods include, but are not limited to, the following: coating a drug or drug-containing composition with an appropriate coating material, typically although not necessarily incorporating a polymeric material, increasing drug particle size, placing the drug within a matrix, and forming complexes of the drug with a suitable complexing agent.

[0073] The delayed release dosage units may be coated with the delayed release polymer coating using conventional techniques, e.g., using a conventional coating pan, an airless spray technique, fluidized bed coating equipment (with or without a Wurster insert), or the like. For detailed information concerning materials, equipment and processes for preparing tablets and delayed release dosage forms, see *Pharmaceutical Dosage Forms: Tablets*, eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989), and *Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems*, 6^{sup}.th Ed. (Media, Pa.: Williams & Wilkins, 1995).

Sustained Release Formulations

[0074] Sustained release matrices are prepared from mixtures of soluble polymers such as ethylcellulose, cellulose acetate, vinyl acetate/vinyl chloride copolymer, acrylate-methacrylate copolymers, polyethylene oxide, hydroxypropyl methylcellulose, carageenan, alginic acid and salts thereof, hydroxyethyl cellulose, hydroxypropyl cellulose, karaya gum, acacia gum, tragacanth gum, locust bean gum, guar gum, sodium carboxymethyl cellulose, methyl cellulose, beeswax, carnauba wax, cetyl alcohol, hydrogenated vegetable oils, stearyl alcohol; and combinations thereof. Carbohydrate particles (non-pareils) can be used as inert cores or carriers in capsule and tablet formulations and are coated by active ingredients. These particles are usually spherical and contain sucrose (62.5%-91.5%) and starch.

[0075] Ion exchange resins suitable for use in granule components are water-insoluble and consist of a pharmaceutically inert organic or inorganic matrix containing

covalently bound functional groups, wherein the functional groups are ionic or capable of being ionized under the appropriate conditions of pH. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (e.g., modified cellulose and dextrans). The inorganic matrix can also be, for example, silica gel modified by the addition of ionic groups. The covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., quaternary ammonium), weakly basic (e.g., primary amine), or a combination of acidic and basic groups. In general, those types of ion exchangers suitable for use in ion exchange chromatography and for such applications as deionization of water are suitable for use in the granule component. Such ion exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp. 312-343), incorporated by reference herein. Useful ion exchange resins generally have exchange capacities below about 6 milliequivalents per gram (meq/g) and preferably below about 5.5 meq/g. The granule ion-exchange resin is cross-linked with a crosslinking agent selected from difunctional compounds capable of cross-linking polystyrenes. The cross-linking agent can be a divinyl or polyvinyl compound. The cross-linking agent can be divinylbenzene. The resin is cross-linked to an extent of about 5 to about 20%, preferably about 4 to about 16%, more preferably about 6 to about 10%, and most preferably about 8% by weight based on the total resin. Representative granule resins include Amberlite® IRI®-60 (Rohm and Haas) and Dow XYS®-40010.00 (Dow Chemical Company). Both are sulfonated polymers composed of polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H-form). Their essential difference is in physical form. Amberlite® IRI®-60 consists of irregularly-shaped particles with a size range of 47 to 149 μ m, produced by 15 milling the parent, large-sized spheres of Amberlite® IRI®-120. The Dow XYS®-40010.00 product consists of spherical particles with a size range of 45 to 150 μ m. Another useful exchange resin, Dow XYS®-40013.00, is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group; its exchange capacity is normally within the range of approximately 3 to 4 meq/g of dry resin.

[0076] *U.S. Pat. Nos.* 2,900,332 to Keating and 4,221,778 to Raghunathan describe adsorption techniques of active drug agents onto ion exchange resin particles to form the drug-resin complex. Briefly, the drug is mixed with an aqueous suspension of the resin, and the complex is then washed and dried. Adsorption of drug onto the resin may be detected by measuring a change in the pH of the reaction medium, or by measuring a change in concentration of sodium or other ions. Binding of drug to resin can be accomplished according to four general reactions. In the case of a basic drug, these are: (a) resin (Na-form) plus drug (salt form); (b) resin (Na-form) plus drug (as free base); (c) resin (H-form) plus drug (salt form); and (d) resin (H-form) plus drug (as free base). All of these reactions except (d) have cationic binding sites by completing with the cationic drug for binding sites on the resin, reduce the amount of drug bound at equilibrium. For basic drugs, stoichiometric binding of drug to resin is accomplished only through reaction (d). Four anionic binding reactions can be carried out for binding an acidic drug to an anion exchange resin. These are:

(a) resin (el-form) plus drug (salt form); (b) resin (Cl-form) plus drug (as free acid); (c) resin (OH-form) plus drug (salt form); and (d) resin (OH-form) plus drug (as free acid). For acidic drugs, stoichiometric binding of drug to resin is accomplished only through reaction (d). The binding may be performed, for example, as a batch or column process, as is known in the art. The drug-resin complex formed is collected and washed with ethanol and/or water to insure removal of any unbound drug. The complexes are usually air-dried in trays at room or elevated temperature. The drug-resin complex has a ratio of active drug(s) to resin of about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1 (by weight).

[0077] C. Formulations

[0078] The devices with different drug release mechanisms described above can be combined in a final dosage form comprising single or multiple units. Examples of multiple units include multilayer tablets, capsules containing tablets, beads, granules, etc. An immediate release portion can be added to the extended release system by means of either applying an immediate release layer up top of the extended release core using coating or compression process or in a multiple unit system such as a capsule containing extended and immediate release beads.

[0079] In one embodiment, a tablet or capsule pharmaceutical formulation includes an anti-tussive agent in an immediate release form, and anti-histamine in an extended release form and a drying agent in a delayed and extended release form.

[0080] In another embodiment, the composition includes a decongestant packed for immediate release; a decongestant packed for extended release, and a drying agent packed for delayed and sustained release, wherein the decongestant provides immediate decongestant relief followed by long-acting decongestant activity, wherein the release of the drying agent is delayed to allow initial decongestion followed by long-acting drying agent activity.

[0081] In another embodiment, a time-release dextromethorphan and a timed release chlorpheniramine are formulated to provide maximum effective release over up to at least 12 hours or more using a combination of polymers in the bead matrix or coat. The drying agent methscopolamine is formulated to provide a 2 to 4 hour delay of release followed by maximum effective release between 4 to 8 hours using a combination of polymers in the bead matrix and coating materials such as pH sensitive polymers or shellac.

Methods of Manufacture

[0082] A preferred method of preparing an extended release tablet is by compressing a drug-containing blend, e.g., blend of granules, prepared using a direct blend, wet-granulation, or dry-granulation process. Extended release tablets may also be molded rather than compressed, starting with a moist material containing a suitable water-soluble lubricant. However, tablets are preferably manufactured using compression rather than molding. A preferred method for forming extended release drug-containing blend is to mix drug particles directly with one or more excipients such as diluents (or fillers), binders, disintegrants, lubricants, glidants, and colorants. As an alternative to direct blending, a drug-containing blend may be prepared by using wet-granulation or dry-granulation processes. Beads containing the active agent may also be prepared by any one of a

number of conventional techniques, typically starting from a fluid dispersion. For example, a typical method for preparing drug-containing beads involves dispersing or dissolving the active agent in a coating suspension or solution containing pharmaceutical excipients such as polyvinylpyrrolidone, methylcellulose, talc, metallic stearates, silicone dioxide, plasticizers or the like. The admixture is used to coat a bead core such as a sugar sphere (or so-called "non-parcel") having a size of approximately 60 to 20 mesh.

[0083] An alternative procedure for preparing drug beads is by blending drug with one or more pharmaceutically acceptable excipients, such as microcrystalline cellulose, lactose, cellulose, polyvinyl pyrrolidone, talc, magnesium stearate, a disintegrant, etc., extruding the blend, spheronizing the extrudate, drying and optionally coating to form the immediate release beads.

[0084] Active pharmaceutical ingredients (API's) can be processed by agglomeration, air suspension drying, balling, coacervation, coating, comminution, compression, cryopelletization, encapsulation, extrusion, wet granulation, dry granulation, homogenization, inclusion complexation, lyophilization, melting, microencapsulation, mixing, molding, pan coating, solvent dehydration, sonication, spheronization, spray drying or other processes known in the art to form granules.

[0085] In a wet granulation method, the at least one pharmaceutically active agent and other ingredients are granulated with a granulating fluid (e.g., isopropyl alcohol, ethyl alcohol, and water) in a planetary mixer, high shear mixer, or a fluid bed granulator. Binding agents may be contained in the granulating fluid, or may be in the dry mix. The wet granules are dried in an oven or fluidized bed dryer, and then sieved through a suitable screen to obtain free flowing granules. The resulting granules are blended with a suitable lubricant and glidant, and the lubricated granules are compressed into tablets on a rotary press using appropriate tooling. If desired, a coating can be applied onto a rotary press using appropriate tooling. If desired, a coating can be applied to the compressed tablets.

[0086] Typical excipients used in these methods include bulking agents, disintegrating agents, anti-adherents and glidants, lubricants, and binding agents. Bulking agents include, but are not limited to, microcrystalline cellulose (e.g., Avicel®; FMC Corp.; Emcoel®; Mendell Inc.), mannitol, xylitol, dicalcium phosphate (e.g., Emcompress®, JRS Pharma) calcium sulfate (e.g., Compactol®, JRS Pharma) starches, lactose, sucrose (Dipac, Amstar, and Nutab, Inc. and Technology), dextrose, sorbitol, cellulose powder (Hercel, Degussa, and Solka Floe, JRS Pharma). The bulking agent may be present in the pharmaceutical composition in an amount of from about 5 wt. % to about 90 wt. %, preferably from about 10 wt. % to about 50 wt. %. Disintegrating agents may be included in the pharmaceutical formulation and include, for example, microcrystalline cellulose, starch, croscopolamide (e.g., Polyplasdone XL®, International Specialty Products), sodium starch glycolate (Explotab®, JRS Pharma) and crosscarmellose sodium (e.g., Ac-Lock®, FMC Corp.). The disintegrating agent may be present in the composition in an amount of from about 0.5 wt. % to about 30 wt. %, preferably from about 1 wt. % to about 10 wt. %. Antiadherents and glidants may be used in the pharmaceutical composition include, for example, talc, silicon starch, silicon dioxide, sodium lauryl sulfate, and metallic stearates. The antiadherent or glidant

may be present in the pharmaceutical formulation in an amount of from about 0.2 wt. % to about 15 wt. %, preferably from about 0.5 wt. % to about 5 wt. %.

[0087] Examples of lubricants used in the excipient mixture include magnesium stearate, calcium stearate, sodium stearate, stearic acid, sodium stearyl fumarate, hydrogenated cotton seed oil (sterotex), talc, and waxes, including but not limited to, beeswax, carnauba wax, cetyl alcohol, glyceryl stearate, glyceryl palmitate, glyceryl behenate, hydrogenated vegetable oils, and stearyl alcohol. The lubricant may be present in an amount of from about 0.2 wt. % to about 20 wt. %, preferably from about 0.5 wt. % to about 5 wt. %. Binding agents include, for example, polyvinyl pyrrolidone, starch, methylcellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, sucrose solution, dextrose solution, acacia, tragacanth and locust bean gum. The binding agent may be present in the composition in an amount of from about 0.2 wt. % to about 10 wt. %, preferably from about 0.5 wt. % to about 5 wt. %. Granules (coated or uncoated) containing active agents are combined with excipients and compressed into a tablet formulation.

[0088] Extended release and delayed release formulations may be prepared and delivered so that release is accomplished in some generally predictable location in the lower intestinal tract more distal than would have accomplished if there had been no delayed release alterations. A method for delay of release is a polymeric coating on each granule intended for extended or delayed release in a more distal portion of the gastrointestinal tract. Any coatings should be applied in sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. Polymers and compatible mixtures thereof may be used to provide the coating for the delayed or the extended release of active ingredients. By way of an example, the sustained release of dextromethorphan, chlorpheniramine, and methscopolamine, over up to at least a 12 hour or more period, was achieved through formulation in a matrix of hydroxypropylmethylcellulose (Methocel® K100M Premium USP Powder), dicalcium phosphate dihydrate, croscarmellose sodium, silicon dioxide, microcrystalline cellulose pH 102 and magnesium stearate. Sustained release granules of methscopolamine, prepared from the same excipients can be coated with pH sensitive polymers that degrade in the lower GI tract, (e.g., Eudragit® L, Eudragit® S, Aquot AS-HF, and ethylcellulose) so that release of active is delayed for 2 to 4 hours until the granule reached the distal ileum colon. The length of the day is controlled by the thickness of coating (amount). Granules can also be coated with shellac. The resulting mixture of granules and excipients can be either compressed into a tablet or filled into a capsule.

[0089] In one embodiment, the compositions include drug-resin complexes having two or three active ingredients. In another embodiment, the invention also provides pharmaceutical compositions including the drug-resins in combination with suitable pharmaceutically acceptable excipients, and optionally at least one of an antihistamine, sympathomimetic drug (nasal decongestant, bronchodilator), analgesic, antiinflammatory, cough suppressant and/or

expectorant. The mean particle size of the granule ion-exchange resins is within the range of about 100 to about 300 μm .

[0090] In another embodiment pharmaceutical combinations include extended release granules of anti-histamines, decongestants, are mixed with delayed and sustained release formulations of drying agents and compressed into rapid dissolving oral tablets. The tablet can further include a binder to permit particles of the porous, plastic substance and the water penetration enhancer to adhere to each other sufficiently to prevent particle segregation and to increase granule adherence at the low pressure used to form the tablet. The binder can include from about 1% to about 90% of the tablet by weight. For example, the binder can be fructose or maltose. The tablet can further include at least one additional ingredient selected from the group consisting of a surfactant, superdisintegrant, superporous hydrogel particle, effervescent agent, lubricant, flavoring agent, a coloring agent and combinations thereof. Some formulations use effervescent couples as their disintegrant, while others use a combination of disintegrants. U.S. Pat. No. 6,596,311 describes different types of non-effervescent disintegrants.

[0091] The formulation can include three active drugs, each within its own granule composition or within the tablet or capsule matrix, wherein the active drugs are an anti-tussive, an antihistamine, and a drying agent. For example, from about 5% to about 20% of the total active anti-tussive is contained within the polymeric material and from about 80% to about 95% is packaged within the extended release granules polymeric material. For example, from about 5% to about 20% of the drying agent is release over the first four hours after dosing, and from about 80% to about 95 percent is released in the period from 4 hours to 24 hours after dosing. For example, from about 5% to about 20% of the total active antihistamine is contained within the rapid dissolve polymeric material and from about 80% to about 95% is packaged within the extended release granules polymeric material. The active anti-tussive can be dextromethorphan, the active antihistamine can be chlorpheniramine. The drying agent can be methscopolamine. The decongestant can be phenylephrine or pseudoephedrine.

EXAMPLE 1

Sustained Release Tablet of Dextromethorphan

[0092] This example provides a sustained release tablet of dextromethorphan, chlorpheniramine and methscopolamine. The tablet was prepared by direct compression of the ingredients listed in Table 1.

TABLE 1

TABLET FORMULATION	
Component	Weight Tablet (mg)
Dextromethorphan hydrobromide	80.60
Chlorpheniramine maleate	8.16
Methscopolamine bromide	2.55
Dicalcium phosphate dihydrate	0.50
Croscarmellose sodium (powder)	22.50
Methocel® K100M Premium USP powder	37.50
Silicon Dioxide	5.00
Microcrystalline Cellulose pH 102	380.69
Magnesium stearate	12.50

[0093] This formulation achieved a sustained release of all actives approximately linearly over a 12 hour period. In formulation that require a delayed release of methscopolamine, sustained release granules of methscopolamine, prepared using excipients shown in Table 1, were coated (10-65% by weight), with the water insoluble and pH sensitive polymers, Eudragit® RS or Eudragit® RL, or combination thereof, using a Wurster Fluidized Bed process. Coated granules of methscopolamine were blended with the other actives and either directly compressed into tablets or filled into capsules.

EXAMPLE 2

Sustained Release Beads of Guaifenesin

[0094] Sustained release beads of guaifenesin were prepared. Briefly, guaifenesin was first granulated with 3% 90F Kollidon® and 0.2% Cab-o-Sil, dried and the mixture passed through a 60/20 mesh screen to collect 200 µm particles. The particles were then placed in a Wurster Fluidized Bed coating machine and coated with a latex dispersion of ethyl cellulose (SURELEASE®, Colorcon). Coated granules were air dried. The ingredients of the coated granules are listed in Table 2 below:

TABLE 2

Component % (by weight)	
Guaifenesin	58.7
SURELEASE®	39.4
90F Kollidon®	1.8
Cab-o-Sil	1.0

Dissolution tests were then carried out on the granules of this example using a standard USP 23NF Drug Release Apparatus filled with 999 ml of the dissolution medium in the vessel and equilibrated to 37° C.±0.5° C. The paddles were set to rotate at 60 RPM. 1 G of granules was added to each vessel. The percent dissolution was determined by HPLC and the results shown in Table 3 below:

TABLE 3

Time (h)	
1	51.2
2	73.6
3	86.1
4	93.3
5	97.0
6	99.3
7	100.1

Additional coating with SURELEASE® prolonged the sustained release of guaifenesin to about 12 hours.

[0095] In formulations that require a delayed release of hydrocodone, the drug plus the sustained release excipients, shown in Table 2, were granulated with 3% 90F Kollidon and 0.2% Cab-o-Sil, sized and then dried. The particles were then coated (~10-65% by weight) with water insoluble polymers Eudragit® RS or Eudragit® RL or combinations thereof, using a Wurster Fluidized Bed coating machine. These granules were then blended with guaifenesin granules and directly compressed into tablets.

EXAMPLE 3

Oral Rapid Dissolving Tablets

[0096] This example illustrates the making of an oral rapid dissolving tablets prepared from sustained release granules

containing chlorpheniramine maleate (8 mg) and phenylephrine HCl (20 µg), and methscopolamine nitrate (2.5 mg). Chlorpheniramine maleate, 90K Kollidon® and Cab-o-sil were mixed and then coated with SURELEASE® to form the first sustained release granules. Delayed release (second) granules having methscopolamine as the active drug and containing 90F Kollidon, Cab-041 were coated with Eudragit® RS or Eudragit® RL or combinations thereof. The coated granules achieved a delayed release of methscopolamine for about 2-4 hours compared to the other actives. Mixtures of first sustained release and second delayed release granules were combined with a fast-dissolving excipient systems, (P-Melt, Fuji Chemical Industry) or Pharmaburst™ (SPI Pharmaceuticals), and then directly compressed into tablets. These tablets dissolved in the oral cavity within 30 seconds. Typically, the final rapid dissolve formulation contained fast-dissolving excipients (~40-70% by weight), sustained and delayed release granules containing actives (~30-60% by weight) and magnesium stearate (~0.4%)

EXAMPLE 4

Sustained Release Beads or Granules

[0097] A capsule was prepared containing sustained release beads or granules of chlorpheniramine maleate and phenylephrine HCl. Delayed release beads or granules of methscopolamine nitrate were added to the capsule formulation.

Formulation 1:

[0098] Chlorpheniramine maleate (30 mg), phenylephrine HCl (15 mg), methscopolamine nitrate (1.25-2.5 mg), non-pareil beads (Sugar Spheres NP of 16-18 mesh cut), Shellac, Eudragit® S, Eudragit® L. Chlorpheniramine maleate and phenylephrine HCl were individually transferred to a coating pan and added to non-pareil beads using Shellac, and allowed to roll and cure for 6 hours before sustained release coating was added. The beads were coated with different amounts of Shellac (ratio of bead mix: Shellac of 1.5:1-2:1) to achieve a sustained release of active for up to 12 hours. After coating the coated beads were at 40° C.

[0099] Beads loaded with methscopolamine were coated together with a first layer of Shellac and then coated again with an outer layer(s) of a mixture of Eudragit® S and Eudragit® L. This results in a delayed release of active drugs for 2 to 4 hours, followed by a sustained release.

Formulation 2:

[0100] Chlorpheniramine maleate (30 mg), phenylephrine HCl (15 mg), methscopolamine nitrate (1.25-2.5 mg), dicalcium phosphate dihydrate, croscarmellose sodium, Methocel K100M premium USP powder, Prosolvic 100 (silicified HPMC; FMC, Pharm), magnesium stearate, Eudragit® S, Eudragit® L are provided in a formulation to first form mini-tabs (Mini Tab Press, SMI) and then load the mixture of mini-tabs into capsules. Chlorpheniramine maleate and phenylephrine HCl are blended with the other excipients and compressed into mini-tabs ~2 mm in length. Methscopola-

mine nitrate is separately blended with excipients including, croscarmellose sodium, Methocel® K100M, magnesium stearate, and Prosolv®, and the blend is compressed into 5 mini-tabs. The mini-tabs are coated with Eudragit® S and Eudragit® L to give a delayed release. Mini-tabs (2 mm in length) are loaded into capsules. Prosolv® is used for the compression of mini-tabs.

Formulation 3: Chlorpheniramine Delayed and Sustained Release Tablets

[0101] Chlorpheniramine maleate (30 mg), phenylephrine HCl (15 mg), methscopolamine nitrate (1.25-2.5 mg), dicalcium phosphate dihydrate (0.5 mg), croscarmellose sodium (22.5 mg), Methocel® K100M premium USP powder (37.5 mg), silicon dioxide (5 mg), microcrystalline cellulose PH102 (380 mg), magnesium stearate (12.5 mg), Eudragit® S, Eudragit® L, are used in a formulation of tablets having both delayed release and sustained release characteristics. Chlorpheniramine maleate and phenylephrine HCl are blended with the above excipients. Methscopolamine nitrate is separately blended with the above excipients and granulated. After drying, the methscopolamine nitrate granules are coated with Eudragit® S/L using a Wurster Fluidized Bed coating machine. The resulting coated methscopolamine granules are introduced into the chlorpheniramine maleate/phenylephrine HCl blend and compressed into tablets. The resulting formulation can achieve a sustained release of chlorpheniramine maleate and phenylephrine HCl over a 12 hours period and a sustained release of methscopolamine nitrate after an initial 2-4 hours delay.

EXAMPLE 5

Sustained Release Formulation

[0102] This example describes a sustained release formulation of a decongestant (guaifenesin) and a cough suppressant (hydrocodone bitartrate). The formulation consists of 1000 mg of guaifenesin, and 10 mg of hydrocodone bitartrate. The formulation is manufactured as a matrix tablet made by direct compression, and contains no immediate release formulation of either guaifenesin or the hydrocodone bitartrate. The tablet is formulated so as to release guaifenesin and hydrocodone over a period of 8 to 12 hours after ingestion. The formulation includes the following standard excipients as shown in Table 4.

TABLE 4

Dicalcium phosphate dihydrate
Croscarmellose sodium
Methocel® K100M
Silicon Dioxide
Microcrystalline cellulose PH 102 (sustained release component)
Magnesium stearate

EXAMPLE 6

Immediate and Sustained Release Formulation

[0103] This example describes a sustained release formulation of a decongestant (guaifenesin) and a cough suppressant (hydrocodone bitartrate) with an immediate release cough suppressant (hydrocodone bitartrate) component. The sustained release formulation core consists of 1000 mg of guaifenesin, and 5 mg of hydrocodone bitartrate. The formulation is manufactured as a matrix tablet made by direct compression, and contains no immediate release formulation

of either guaifenesin or the hydrocodone bitartrate. The tablet is formulated so as to release guaifenesin and hydrocodone over a period of 8 to 12 hours after ingestion. The formulation includes the following standard excipients:

- [0104] Dicalcium phosphate dihydrate
- [0105] Croscarmellose sodium
- [0106] Methocel® K100M
- [0107] Silicon Dioxide
- [0108] Microcrystalline cellulose PH 102 (sustained release component)
- [0109] Magnesium stearate

[0110] The sustained release core is coated with an immediate release film containing 5 mg cough suppressant (hydrocodone bitartrate) by processes readily known to those skilled in the art.

EXAMPLE 7

Sustained Release Granules

[0111] This example provides a matrix tablet of sustained release granules in the form of bead manufactured by direct compression that provides a release profile of sustained release of guaifenesin and hydrocodone over a period of 8 to 12 hours after ingestion. The formulations are designed such that 10 to 20% of the hydrocodone is released within the first 4 hours after ingestion, and 80 to 90% of the hydrocodone is released between 4 to 12 hours after ingestion. There are no separate immediate release guaifenesin components in the formulations. Variation in the properties of the guaifenesin and hydrocodone formulations are achieved by adjusting the composition and thickness of the granule coatings and the composition of the tableting excipients to vary the release profile of sustained release guaifenesin followed by a sustained release of hydrocodone after the initial delay of approximately 4 hours.

Formulation 1

[0112] Formulation 1 can be manufactured by first wet mixing (granulating) guaifenesin and hydroxypropyl methylcellulose, in a high-energy high-shear mixer to produce dense guaifenesin pellets. In a similar process hydrocodone and hydroxypropyl methylcellulose is mixed to produce dense hydrocodone pellets. The resulting guaifenesin and hydrocodone pellets are sieved to the same size. The pellets are then combined and mixed with more hydroxypropyl methylcellulose and compressed into tablets. The resulting tablets are then formed by a mixture of hydroxypropyl methylcellulose, guaifenesin granulation, hydroxypropyl methylcellulose, hydrocodone granulation and additional hydroxypropyl methylcellulose.

[0113] Once the formulations are swallowed or consumed, the tablets become wet and the hydroxypropyl methylcellulose surrounding the tablets is believed to form thin gel layers. Any immediate guaifenesin exposed to the exterior of the tablets will dissolve out of the tablets, resulting in an immediate release of guaifenesin for absorption. As the guaifenesin on the outer surfaces of the tablets, gastric fluid will reach deeper into the tablets, resulting in a slower dissolution and the dissolution of the intermediate release guaifenesin granules surrounded by the gel layers. The gel layers then act as controlled release layers for delayed guaifenesin originating in the intermediate release granules. Erosion of the gel layers results in further drug release. Hydrocodone is released in a similar fashion from hydrocodone granules.

[0114] Additional polymers such as hydroxypropyl methylcellulose of differing molecular weights or ethylcellulose in the hydrocodone granules are added to delay the release of hydrocodone for approximately 4 hours. An exemplary swelling agent is hydroxypropyl methylcellulose, in an amount ranging from about 5% to about 50% parts by weight per 100 parts by weight of tablet or formulation.

[0115] The formulation ensures sustained time release over a period of approximately 8 to 12 hours as demonstrated by in vitro dissolution techniques known to those skilled in the art. A binder may also be employed, preferably a material such as one or more of a group of polymers having the repeating unit of 1-ethenyl-2-pyrrolidinone. These polymers generally have molecular weights of between about 10,000 and 700,000 Daltons, and are also known as "povidone". Amounts of the binder material will vary depending upon the nature of the binder and the amount of other ingredients of the compositions. An exemplary amount of povidone is from about 1% to about 5% by weight of povidone per 100 parts by weight of the total formulation. Processing aids such as lubricants, including stearic acid, may also be employed, as is known in the art. An exemplary amount of stearic acid is from about 0.5% to about 2.0% by weight per 100 parts by weight of table or formulation. One composition of formulation 1 is provided in Table 4:

TABLE 4

Tablet Composition	Ingredient Weight (mg)
Guaifenesin	1000
Hydrocodone	10
Hydroxypropyl methylcellulose	406
Povidone	35
Stearic Acid	15
TOTAL	1466

[0116] Granulation Process Description

[0117] The unprocessed guaifenesin and hydrocodone raw materials are dispensed and granulated in a high shear granulator. The wet granules are sieved into a fluid bed drier and dried. When the drying process is complete, the granules are milled. Milling ensures uniform particle size distribution throughout the guaifenesin and hydrocodone granules.

[0118] Tablet Process Description

[0119] The guaifenesin and hydrocodone tablet blend is manufactured by blending the guaifenesin and hydrocodone granulations, extragranular Methocel® E10M and Hystrene® 5016 (Stearic acid). A guaifenesin and hydrocodone tablet blend is compressed to form guaifenesin and hydrocodone tablets.

[0120] Manufacturing Process

[0121] The guaifenesin and hydrocodone tablets may be manufactured by the following possible manufacturing process. A Littleford® FM130 granulator is charged with approximately one half of the guaifenesin, USP required for the process unit (about 17.4 kg) followed by about 4.00 kg of Methocel®, USP E10M Premium CR Grade; and 1.20 kg of Povidine, USP; and the balance of the guaifenesin (about 17.40 kg). The powder bed is dry mixed in the Littleford® FM130 granulator, with choppers on, for approximately 1 minute. At the completion of the 1-minute pre-mix cycle, about 12.0±0.05 kg of Purified Water, USP are sprayed onto the powder bed at a rate of about 2.40±0.24 kg/minute. Immediately following the addition of the Purified Water,

USP, the unit is granulated for about 5 minutes. Hydrocodone granules are processed in a similar fashion. The granulated unit is discharged into double polyethylene-lined containers and then manually loaded into a Glatt® bowl while being passed through a #4 mesh screen. The Glatt® bowl is loaded into a Glatt TFO-60 fluid-bed drier with an inlet air temperature setting of about 70° C.±0.5° C. The unit is dried until a moisture level of 0.1±1.0% is obtained as determined using a Computrac® Moisture Analyzer, model NASA. The dried granulation is discharged into appropriately labeled, double polyethylene-lined drums and reconciled. The dried and reconciled granulation is then passed through a Kemtec® BetaGrind mill equipped with a 1.5 mm screen and running at approximately 1500 RPM. The milled granulation is collected into appropriately labeled, double polyethylene-lined drums and reconciled. The milled granulation is sampled and tested by Quality Control and released prior to further processing. The released guaifenesin and hydrocodone granulation units are charged to a Patterson-Kelley 20 ft3 V-blender after which they are blended together for about 10±1 minutes and then discharged to appropriately labeled, double polyethylene-lined containers.

[0122] Guaifenesin and hydrocodone tablets are formulated from a common granulation which is blended with appropriate quantities of Methocel®, USP E10M Premium CR Grade and Stearic Acid, NF to achieve a final dosage formulation.

[0123] Dense pellets of guaifenesin and hydrocodone are prepared according to the wet granulation procedure for Formulation 1 as described in Example 7. Sized granules of guaifenesin are coated with an aqueous ethylcellulose dispersion (SOLUBLEBASE™) in a fluid bed with Wurster configuration, using a temperature of 42-44° C., and a spray rate of 0.5 g/min. Delayed release granules of hydrocodone are coated with a latex dispersion of acrylic acid polymers (Coatdrag® RS) in a fluid bed with Wurster configuration. Guaifenesin and hydrocodone tablets are then manufactured as in Formulation 1.

[0124] Modifications and variations of the present invention will be apparent to those skilled in the art. The scope of the present description and are intended to be encompassed by the following claims. All references cited herein are specifically incorporated by reference.

1. A method of preparing a tablet comprising:

- a. dry mixing a composition for a tablet comprising two or more drugs acting on different symptoms;
- b. granulating the composition for a combination of immediate release, controlled release, and delayed release where the first drug is immediately released prior to release of the second or more drugs to produce an effect that enhances action of the second drug;
- c. compressing the composition of claim 1, wherein the two or more drugs are selected from the group consisting of: decongestants, antitussives, expectorants, antihistamines, cough suppressants, drying agents, and combination thereof;
- d. granulating the composition of claim 2, wherein the cough suppressant is selected from the group consisting of: dextromethorphan, pseudoephedrine, and combination thereof; and
- e. compressing the composition of claim 2, wherein the antitussive is selected from the group consisting of: dextromethorphan, benzonatate, and combination thereof.

niramine, triprolidine, diphenhydramine, doxylamine, tripe-
lenamine, cyproheptadine, bromodiphenhydramine, phen-
indamine, pyrilamine, azatadine, pharmaceutically
acceptable salts thereof and combinations thereof.

5. The composition of claim 2, wherein the expectorant is
selected from the group consisting of guaifenesin, terpin
hydrate, (glyceryl guaiacolate), potassium guaiacolsul-
fonate, pharmaceutically acceptable salts thereof, and com-
binations thereof.

6. The composition of claim 2, wherein the antitussive is
selected from the group consisting of caramiphen, dex-
tromethorphan, codeine, hydrocodone, pharmaceutically
acceptable salts thereof, and combinations thereof.

7. The composition of claim 2, wherein drying agent is
selected from the group consisting of methscopolamine,
scopolamine, meclizine, trimethobenzamide, dimenhydi-
nate, cyclizine, pheniramine, buclizine, chlorpheniramine,
diphenhydramine, homatropine, carbinoxamine, clemastine,
brompheniramine, and doxylamine.

8. The composition of claim 2, wherein the cough sup-
pressant is selected from the group consisting of benzonat-
ate, bromodiphenhydramine, brompheniramine, buclizine,
carbinoxamine, chlorpheniramine, clemastine, codeine,
cyclizine, dexchlorpheniramine, dextromethorphan, dihy-
drocodeine, dimenhydrinate, diphenhydramine, doxy-
lamine, homatropine, hydrocodone, meclizine, pheniramine,
phenyltoloxamine, pyrilamine, trimethobenzamide, triproli-
dine.

9. The composition of claim 2 comprising an expectorant
of immediate and extended release, wherein over 90% of the
drug is released substantially linearly over a 12 hour period
of time, and a cough suppressant for delayed and extended
release, wherein over 90% of the drug is released between
4 and 12 hours, wherein the release profiles of the ingredi-
ents are orchestrated to coordinate the production and clear-
ance of mucus and cough suppression.

10. The composition of claim 2 comprising:

- (a) an anti-tussive active drug within a granule matrix
packaged for extended release of over 90% of the
active drug released substantially linearly over a 12
hour period of time;
- (b) an anti-histamine active drug packaged for extended
release of over 90% of the active drug released sub-
stantially linearly over a 12 hour period of time; and
- (c) a drying agent active drug packaged for delayed and
extended release of over 90% of the active drug
released substantially linearly over a period of 8 hours
following an initial delay of release of from about two
to about four hours.

11. A composition of claim 2 wherein the pharmaceutical
composition comprises:

- (a) an immediate release decongestant active drug pack-
aged for immediate release of over 60-80% of the
active drug within from about 90 minutes to about 120
minutes following dosing;
- (b) an extended release decongestant active drug pack-
aged for extended release of over 90% of the active
drug released substantially linearly over a 12 hour
period of time; and
- (c) a drying agent active drug packaged for delayed and
extended release of over 90% of the active drug
released substantially linearly over an 8 hour period
following an initial delay of release of from about two
to about 4 hours.

12. The composition of claim 9 wherein the pharmaceu-
tical composition includes:

- (a) an immediate release expectorant active drug pack-
aged for immediate release of over 60-80% of the
active drug within from about 90 minutes to about 120
minutes following dosing;
- (b) an extended release expectorant active drug packaged
for extended release of over 90% of the active drug
released substantially linearly over up to at least a 12
hour period of time;
- (c) an antitussive active drug packaged for delayed and
extended release of over 90% of the antitussive active
drug released substantially linearly over up to at least
an 8 hour period following an initial delay of release of
from about 2 to about 4 hours; and
- (d) optionally a drying agent active drug packaged for
delayed and extended release of over 90% of the active
drug released substantially linearly over up to at least
an 8 hour period following an initial delay of release of
from about 2 to about 4 hours.

13. The composition of claim 9 wherein the pharmaceu-
tical composition includes:

- (a) an immediate release expectorant active drug pack-
aged for immediate release of over 60-80% of the
active drug within from about 90 minutes to about 120
minutes following dosing;
- (b) an extended release expectorant active drug packaged
for extended release of over 90% of the active drug
released substantially linearly over up to at least a 12
hour period of time;
- (c) an antitussive active drug packaged for delayed and
extended release of over 90% of the active drug
released substantially linearly over up to at least an 8
hour period following an initial delay of release of from
about 2 to about 4 hours; and
- (d) optionally a drying agent active drug packaged for
delayed and extended release of over 90% of the active
drug released substantially linearly over up to at least
an 8 hour period following an initial delay of release of
from about 2 to about 4 hours.

14. The composition of claim 9 wherein the pharmaceu-
tical composition includes:

- (a) an extended release expectorant active drug packaged
for extended release of over 90% of the expectorant
active drug released substantially linearly over up to at
least a 12 hour period of time; and
- (b) an antitussive active drug packaged for delayed and
extended release, wherein over 90% of the antitussive
active drug is released substantially linearly over up to
at least an 8 hour period following an initial delay of
release of from about 2 to about 4 hours.

15. The composition of claim 9 wherein the pharmaceu-
tical composition includes:

- (a) an extended release expectorant active drug packaged
for extended release of over 90% of the expectorant
active drug released substantially linearly over up to at
least a 12 hour period of time; and
- (b) an antitussive active drug packaged for sustained
release such that up to 20% of the antitussive active
drug is released within sustained release over the first
1 to 4 hours followed by the sustained release of up to
100% of the antitussive active drug between 4 to 12
hours.

16. The composition of claim 9 wherein the pharmaceutical composition includes:

- (a) an extended release expectorant active drug packaged for extended release of over 90% of the expectorant active drug released substantially linearly over up to at least a 12 hour period of time; and
- (b) an antitussive active drug packaged for sustained release wherein the antitussive active drug is released in a first immediate release pulse, such that up to 50% of the antitussive active drug is released in a sustained fashion over the first 1 to 4 hours, followed by a sequential immediate release pulse of the antitussive active drug, such that up to 100% of the antitussive active drug is released between 4 to 6 hours.

17. The composition of claim 9 wherein the pharmaceutical composition includes:

- (a) an extended release expectorant active drug packaged for extended release of over 90% of the expectorant active drug released substantially linearly over up to at least a 12 hour period of time; and
- (b) an antitussive active drug packaged for immediate and sustained release, such that up to 50% of the antitussive active drug is released in immediate fashion over the first 1 to 4 hours, followed by sustained release of the antitussive drug, such that up to 100% of the antitussive active drug is released between 4 to 12 hours.

18. The composition of claim 9 wherein the pharmaceutical composition includes:

- (a) an extended release expectorant active drug packaged for extended release, wherein 20 to 35% of the expectorant active drug is released between 0 to 20 hours, 35-65% of the expectorant active drug is released between 2 to 4 hours, and 65-90% of the expectorant active drug is released between 4 to 8 hours; and

an antitussive active drug.

19. The composition of claim 9, wherein the pharmaceutical formulation is in a form selected from the group consisting of a capsule, tablet, oral rapid dissolving tablet, softgel, gelcap, film, gum, pastille, lozenge, disk, and wafer.

20. The composition of claim 9 wherein the anti-tussive active drug is dextromethorphan in the form selected from the group consisting of an immediate release bead, an immediate release matrix, a sustained release bead, a sustained release matrix, and combinations thereof; the antihistamine active drug is chlorpheniramine in a form selected from the group consisting of an immediate release bead, an immediate release matrix, a sustained release bead, a sustained release matrix, and combinations thereof; and the drying agent active drug is methscopolamine in a form selected from the group consisting of an immediate release bead, an immediate release matrix, a sustained release bead, a sustained release matrix, and combinations thereof.

21. The composition of claim 9 wherein the decongestant is pseudoephedrine in the form selected from the group consisting of an immediate release bead, an immediate

release matrix, a sustained release bead, a sustained release matrix, and combinations thereof.

22. The composition of claim 9 wherein the expectorant is guaifenesin in the form selected from the group consisting of an immediate release bead, an immediate release matrix, a sustained release bead, a sustained release matrix, and combinations thereof.

23. The composition of claim 9 wherein the antitussive is hydrocodone in a form selected from the group consisting of an immediate release bead, an immediate release matrix, a sustained release bead, a sustained release matrix, and combinations thereof.

24. The composition of claim 9 wherein the tablet is in the form of a rapid dissolving tablet.

25. The composition of claim 9, comprising different types of coated beads or granules into a capsule, wherein each type of coated bead or granule includes individually an extended release antitussive, an extended release antihistamine and drying agent in a delayed release form, and wherein the capsule further includes one or more excipients.

26. The composition of claim 9, comprising a mixture of excipients and a mixture of granules into a tablet, wherein each type of granule includes individually an extended release antitussive, an extended release antihistamine and a drying agent in a delayed release form.

27. The composition of claim 9 wherein the mixture of excipients further includes free active drug.

28. The composition of claim 9 comprising a formulation of hydrocodone and guaifenesin, wherein release of hydrocodone is achieved by a series of sequential immediate release pulses for up to 12 hours after administration.

29. The composition of claim 9 comprising hydrocodone and guaifenesin in claim 9, wherein 25-50% of the hydrocodone is released in an immediate release pulse within 1-4 hours after administration and 50-100% of the hydrocodone is released as a second immediate release pulse within 4 to 12 hours after administration.

30. The composition of claim 9 comprising hydrocodone and guaifenesin in claim 9, wherein up to 100% of the hydrocodone is released as a single immediate release component 2 to 12 hours after administration.

31. The composition of claim 9, comprising hydrocodone and guaifenesin wherein 25-50% of the hydrocodone is released in a sustained fashion during the first 1 to 4 hours after administration, which is followed by a second release of up to 100% of the hydrocodone between 4 to 12 hours after administration.

32. The composition of claim 9 comprising hydrocodone and guaifenesin wherein (i) 20 to 35% of the hydrocodone is released within 2 hours of administration, (ii) 35-65% is released between 2 to 4 hours after administration and (iii) 65-90% is released between 4 to 8 hours after administration.

* * *

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

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

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por escritura pública número 2670 de la Notaría Segunda de Cali de fecha 12 de
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expedido por la Cámara de Comercio de Cali -----

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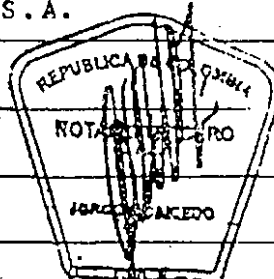
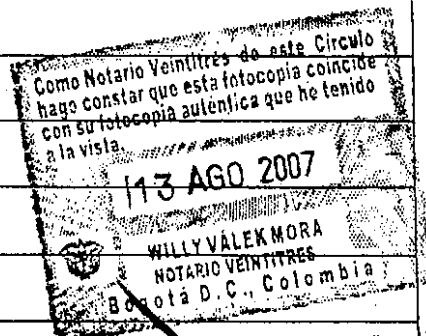
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

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

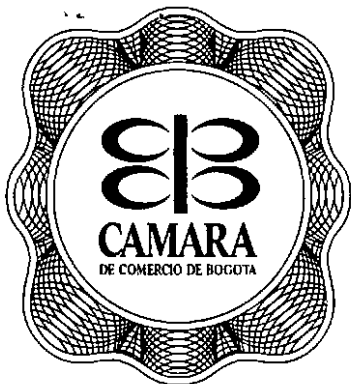
En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

REPUBLICA DE COLOMBIA
FCE
DILIGENCIA DE AUTENTICACIÓN
El Notario del Circulo de Bogotá D.C. que esta en la Oficina de Notaría Pública y DA FE que esta fotocopia coincide con la copia autenticada que tuvo a la vista
19 DIC 2011
NOTARIO CUARENTA Y CINCO



40

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 1

CERTIFICA:

NOMBRE: TECNOQUIMICAS S.A.

SIGLA : TQ S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : CL. 23 NRO. 7 39

DIRECCION NOTIFICACION JUDICIAL: CL. 23 NRO. 7 39

CIUDAD: CALI

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

CERTIFICA:

NIT : 890300466-5

CERTIFICA:

QUE POR ESCRITURA NRO. 2670 DEL 12 DE JUNIO DE 1957 NOTARIA SEGUNDA DE CALI ,
INSCRITA EN LA CAMARA DE COMERCIO EL 01 DE JULIO DE 1957 BAJO EL NRO. 16627
DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA COMPAÑIAS 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 , SE TRANSFORMO DE SOCIEDAD LIMITADA EN SOCIEDAD EN
COMANDITA POR ACCIONES BAJO EL NOMBRE DE COMPAÑIAS TECNOQUIMICAS LIMITADA
COMANDITA POR ACCIONES (SIC) .

CERTIFICA:

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

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 , SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES EN SOCIEDAD
ANÓNIMA 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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 2

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 , CAMBIO SU NOMBRE DE TECNOQUIMICAS S A . POR EL DE TECNOQUIMICAS S. A. . SIGLA: TQ S.A.

CERTIFICA:

QUE POR ESCRITURA NRO. 4551 DEL 23 DE OCTUBRE DE 2008 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 04 DE NOVIEMBRE DE 2008 BAJO EL NRO. 12416 DEL LIBRO IX ,SE APROBO LA ESCISION PARCIAL DEL PATRIMONIO SOCIAL ENTRE (ESCINDENTE) TECNOQUIMICAS S.A. Y (BENEFICIARIA(S)) INVERSIONES TQTS S. A. .

CERTIFICA:

REFORMAS

DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO				
E.P. 4075 16922	05/09/1957	NOTARIA SEGUNDA DE CALI	27/09/1957	
E.P. 5718 17242	28/11/1957	NOTARIA SEGUNDA DE CALI	30/12/1957	
E.P. 5507 17529	31/12/1957	NOTARIA PRIMERA DE CALI	13/03/1958	
E.P. 3124 18365	16/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
E.P. 3325 18366	29/07/1958	NOTARIA PRIMERA DE CALI	17/10/1958	
E.P. 5726 19258	17/12/1958	NOTARIA PRIMERA DE CALI	12/05/1959	
E.P. 2374 19368	12/05/1959	NOTARIA PRIMERA DE CALI	03/06/1959	
E.P. 2793 22616	20/06/1961	NOTARIA PRIMERA DE CALI	07/07/1961	

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 3

E.P. 2794 22617	20/06/1961	NOTARIA	PRIMERA	DE	CALI	07/07/1961
E.P. 6365 23489	30/12/1961	NOTARIA	PRIMERA	DE	CALI	23/01/1962
E.P. 1383 23850	21/03/1962	NOTARIA	PRIMERA	DE	CALI	28/03/1962
E.P. 3396 26016	28/05/1963	NOTARIA	PRIMERA	DE	CALI	11/06/1963
E.P. 8853 27107	30/12/1963	NOTARIA	PRIMERA	DE	CALI	23/01/1964
E.P. 5718 27181	28/11/1957	NOTARIA	SEGUNDA	DE	CALI	10/02/1964
E.P. 2743 27681	29/04/1964	NOTARIA	PRIMERA	DE	CALI	06/05/1964
E.P. 2744 27682	29/04/1964	NOTARIA	PRIMERA	DE	CALI	06/05/1964
E.P. 7057 28591	21/10/1964	NOTARIA	PRIMERA	DE	CALI	22/10/1964
E.P. 1693 29569	26/04/1965	NOTARIA	PRIMERA	DE	CALI	28/04/1965
E.P. 1799 31623	10/05/1966	NOTARIA	PRIMERA	DE	CALI	11/05/1966
E.P. 2498 32757	18/11/1966	NOTARIA	CUARTA	DE	CALI	25/11/1966
E.P. 2792 33009	27/12/1966	NOTARIA	CUARTA	DE	CALI	05/01/1967
E.P. 2209 34591	25/09/1967	NOTARIA	CUARTA	DE	CALI	04/10/1967
E.P. 6933 35082	20/12/1967	NOTARIA	SEGUNDA	DE	CALI	28/12/1967
E.P. 6363 37141	14/11/1968	NOTARIA	SEGUNDA	DE	CALI	26/11/1968
E.P. 7711 37615	31/12/1968	NOTARIA	SEGUNDA	DE	CALI	04/02/1969
E.P. 5597	30/09/1969	NOTARIA	SEGUNDA	DE	CALI	18/10/1969

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 4

39341

E.P. 5211 27/08/1970 NOTARIA SEGUNDA DE CALI 04/09/1970

41379

E.P. 6576 07/10/1971 NOTARIA SEGUNDA DE CALI 14/10/1971

44154

E.P. 7286 08/11/1971 NOTARIA SEGUNDA DE CALI 10/11/1971

44367

E.P. 8042 03/12/1971 NOTARIA SEGUNDA DE CALI 21/12/1971

44716

E.P. 6209 05/10/1973 NOTARIA SEGUNDA DE CALI 15/10/1973

5505 IX

E.P. 8741 31/12/1973 NOTARIA SEGUNDA DE CALI 08/03/1974

7636 IX

E.P. 9270 31/12/1974 NOTARIA SEGUNDA DE CALI 31/01/1975

11772 IX

E.P. 9504 31/12/1974 NOTARIA SEGUNDA DE CALI 04/04/1975

12441 IX

E.P. 7566 05/12/1975 NOTARIA SEGUNDA DE CALI 09/01/1976

15581 IX

E.P. 2671 09/05/1980 NOTARIA SEGUNDA DE CALI 22/10/1980

41529 IX

E.P. 779 10/03/1982 NOTARIA DECIMA DE CALI 03/08/1982

54655 IX

E.P. 4324 10/11/1982 NOTARIA DECIMA DE CALI 30/06/1983

61172 IX

E.P. 1269 18/03/1986 NOTARIA DECIMA DE CALI 01/04/1986

83730 IX

E.P. 5089 24/09/1986 NOTARIA DECIMA DE CALI 29/09/1986

87933 IX

E.P. 7064 04/11/1987 NOTARIA DECIMA DE CALI 19/11/1987

2552 IX

E.P. 7065 04/11/1987 NOTARIA DECIMA DE CALI 19/11/1987

2553 IX

E.P. 5929 14/07/1989 NOTARIA DECIMA DE CALI 26/07/1989

20225 IX

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 5

E.P. 8569 22250 IX	29/09/1989	NOTARIA	DECIMA	DE	CALI	02/10/1989
E.P. 10571 60929 IX	04/12/1992	NOTARIA	DECIMA	DE	CALI	15/12/1992
E.P. 10249 10214 IX	18/12/1995	NOTARIA	DECIMA	DE	CALI	20/12/1995
E.P. 2359 3813 IX	22/05/1997	NOTARIA	TERCERA	DE	CALI	27/05/1997
E.P. 2624 4740 IX	30/06/2000	NOTARIA	TERCERA	DE	CALI	07/07/2000
E.P. 3814 6381 IX	15/09/2000	NOTARIA	TERCERA	DE	CALI	18/09/2000
E.P. 3588 8542 IX	30/07/2004	NOTARIA	TERCERA	DE	CALI	04/08/2004
E.P. 2224 6565 IX	24/05/2006	NOTARIA	TERCERA	DE	CALI	30/05/2006
E.P. 1675 5362 IX	08/05/2008	NOTARIA	TERCERA	DE	CALI	16/05/2008
E.P. 4551 12416 IX	23/10/2008	NOTARIA	TERCERA	DE	CALI	04/11/2008
E.P. 917 2978 IX	05/03/2009	NOTARIA	TERCERA	DE	CALI	13/03/2009
E.P. 1809 5625 IX	05/05/2009	NOTARIA	TERCERA	DE	CALI	15/05/2009
E.P. 5409 14004 IX	01/12/2009	NOTARIA	TERCERA	DE	CALI	07/12/2009
E.P. 2465 7575 IX	18/06/2010	NOTARIA	TERCERA	DE	CALI	25/06/2010

CERTIFICA:

VIGENCIA: 01 DE ENERO DEL AÑO 2057

CERTIFICA:

OBJETO SOCIAL. LA SOCIEDAD TIENE POR OBJETO: A) LA FABRICACION, EL ENVASADO, LA IMPORTACION, LA EXPORTACION, LA VENTA Y DISTRIBUCION DE PRODUCTOS BIOLÓGICOS Y QUÍMICOS, MEDICAMENTOS O PRODUCTOS FARMACÉUTICOS, PERFUMERIA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS, AGRÍCOLAS Y ALIMENTOS NATURALES

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 6

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

QUE EN LA ESCRITURA PUBLICA NRO. 5409 DE REFORMA CITADA, SE ADICIONA AL ARTICULO 4 DE LOS ESTATUTOS SOCIALES EL LITERAL G) EN LOS SIGUIENTES TERMINOS:

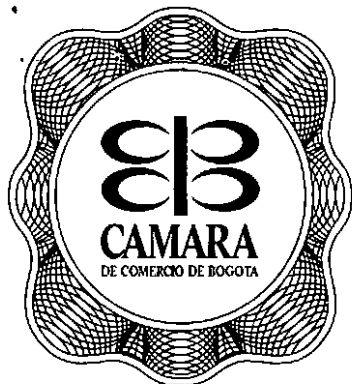
i) LA PRESTACION DE SERVICIOS RELACIONADOS CON EL CUIDADO DE BEBES, INCLUIDOS SERVICIOS DE GUARDERIA, SALA CUNA Y SIMILARES.

ii) LA PRESTACION DE SERVICIOS RELACIONADOS CON LA INVESTIGACION DE MERCADOS EN BENEFICIO DE NEGOCIOS PROPIOS O DISTRIBUIDOS.

CERTIFICA:

ÓRGANOS DE DIRECCIÓN Y ADMINISTRACIÓN. PARA LOS FINES DE SU DIRECCIÓN, ADMINISTRACIÓN Y REPRESENTACIÓN, LA SOCIEDAD TIENE LOS SIGUIENTES ÓRGANOS: A)

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43

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 7

ASAMBLEA GENERAL DE ACCIONISTAS. B) JUNTA DIRECTIVA. C) PRESIDENTE EJECUTIVO. D) DOS VICEPRESIDENTES EJECUTIVOS. E) VICEPRESIDENCIAS ADMINISTRATIVAS. LA DIRECCIÓN 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 REPRESENTACIÓN LEGAL DE LA SOCIEDAD Y LA GESTIÓN DE LOS NEGOCIOS SOCIALES, ESTARÁN A CARGO DEL PRESIDENTE EJECUTIVO Y DE LOS DOS VICEPRESIDENTES EJECUTIVOS. LAS VICEPRESIDENCIAS ADMINISTRATIVAS SON ORGANOS ESPECIALES CREADOS POR LA ASAMBLEA EN BENEFICIO DE LA COMPAÑIA Y EL NOMBRAMIENTO DE QUIENES SEAN DESIGNADOS, SU NUMERO, FACULTADES Y ATRIBUCIONES QUE EJERCERAN SE CONFIEREN EN SU REGLAMENTACION Y EJECUCION, COMO NORMA ESPECIAL, A LA JUNTA DIRECTIVA QUE LAS DETERMINARÁ DE CONFORMIDAD ESTOS ESTATUTOS, A LA ORGANIZACIÓN ADMINISTRATIVA QUE POR ORIENTACIÓN SE LE QUIERE DAR A LA SOCIEDAD Y POR LA LEY.

FUNCIONES DE LA ASAMBLEA DE ACCIONISTAS. ENTRE OTRAS LAS SIGUIENTES: 1) ACORDAR LA FUSIÓN DE LA SOCIEDAD, SU TRANSFORMACIÓN, LA ENAJENACIÓN O EL ARRENDAMIENTO DE LA EMPRESA SOCIAL, LA DISOLUCIÓN O LA PRORROGA Y CUALQUIER REFORMA, AMPLIACIÓN MODIFICACIÓN DEL CONTRATO SOCIAL. 9) AUTORIZAR LA ADQUISICIÓN DE ACCIONES PROPIAS, CON SUJECCIÓN A LOS REQUISITOS ESTABLECIDOS POR LA LEY. 10) ADOPTAR EN GENERAL, TODAS LAS MEDIDAS QUE RECLAMEN EL CUMPLIMIENTO DE LOS ESTATUTOS O EL INTERÉS DE LA SOCIEDAD.

LA JUNTA DIRECTIVA SE COMPONE DE NUEVE (9) MIEMBROS PRINCIPALES O DIRECTORES, ELEGIDOS POR LA ASAMBLEA GENERAL DE ACCIONISTAS PARA PERÍODOS DE DOS AÑOS, SIN PERJUICIO DE QUE PUEDAN SER REMOVIDOS LIBREMENTE POR LA ASAMBLEA O REELEGIDOS INDEFINIDAMENTE. SIMULTÁNEAMENTE CON LA ELECCIÓN DE LOS PRINCIPALES LA ASAMBLEA ELEGIRÁ NUEVE (9) SUPLENTE PERSONALES LOS CUALES REEMPLAZARÁN A LOS RESPECTIVOS PRINCIPALES EN SUS FALTAS ABSOLUTAS, ACCIDENTALES O TEMPORALES.

PARÁGRAFO. CUANDO LA ELECCIÓN DE PRINCIPALES Y SUPLENTE SE HUBIERE EFECTUADO CON BASE EN MÁS DE UNA LISTA, LOS SUPLENTE REEMPLAZARÁN A LOS PRINCIPALES ELEGIDOS POR LA MISMA LISTA. AL EFECTUAR LA ELECCIÓN DE LOS MIEMBROS PRINCIPALES Y SUPLENTE LA ASAMBLEA DE ACCIONISTAS DETERMINARÁ DE ACUERDO CON LOS RESULTADOS DEL ESCRUTINIO, EL ORDEN DE PRECEDENCIA DE UNOS Y OTROS.

EN LA JUNTA DIRECTIVA SE ENTIENDE DELEGADO EL MAS AMPLIO MANDATO PARA ADMINISTRAR LA SOCIEDAD Y POR CONSIGUIENTE, TENDRÁ ATRIBUCIONES SUFICIENTES PARA ORDENAR QUE SE EJECUTE O CELEBRE CUALQUIER ACTO O CONTRATO COMPRENDIDO

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 8

DENTRO DEL OBJETO SOCIAL Y PARA ADOPTAR LAS DETERMINACIONES NECESARIAS EN ORDEN A QUE LA SOCIEDAD CUMPLA SUS FINES Y DE MANERA ESPECIAL, TENDRÁ 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 POLÍTICAS DE LA SOCIEDAD EN LOS DIFERENTES ORDENES DE SU ACTIVIDAD, ESPECIALMENTE EN MATERIA FINANCIERA, ECONÓMICA Y LABORAL; APROBAR PLANES DE INVERSIÓN Y DE PRODUCCIÓN; DECIDIR SOBRE NUEVAS LINEAS DE PRODUCCIÓN Y VENTA, ESTABLECER NORMAS GENERALES EN MATERIA DE PRECIOS Y DE VENTAS DE LOS PRODUCTOS ELABORADOS POR LA SOCIEDAD O DE LOS MATERIALES Y DEMÁS ELEMENTOS EN QUE ELLA NEGOCIE Y DICTAR NORMAS Y REGLAMENTOS PARA LA ORGANIZACIÓN Y EL FUNCIONAMIENTO DE TODAS LAS DEPENDENCIAS DE LA SOCIEDAD.

G) DETERMINAR LA APLICACIÓN QUE DEBA DARSE A LAS UTILIDADES QUE, CON EL CARÁCTER DE RESERVAS DE INVERSIÓN, 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 RAÍCES, CUALQUIERA QUE SEA SU CUANTÍA.

2) CONSTITUIR PRENDA SOBRE BIENES SOCIALES O DARLOS EN ANTICRESIS PARA ACTOS O CONTRATOS CUYA CUANTÍA 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 CUANTÍA IGUAL O SUPERIOR A CIEN MIL DÓLARES DE USA (\$US100.000.00).

4) AUTORIZAR LOS CONTRATOS DE MUTUO QUE PUEDAN CELEBRAR LA SOCIEDAD, LOS REPRESENTANTES LEGALES CUANDO SU CUANTÍA SEA SUPERIOR A \$100.000.000.00 MONEDA LEGAL COLOMBIANA O A TRESCIENTOS MIL DÓLARES DE USA (\$US300.000.00).

PARAGRAFO: NO OBSTANTE LO ANTERIOR, LOS REPRESENTANTES LEGALES PODRÁN CELEBRAR ILIMITADAMENTE, SIN NECESIDAD DE APROBACIÓN PREVIA DE LA JUNTA DIRECTIVA, CONTRATOS RELACIONADOS CON LICENCIAS, AGENCIA COMERCIAL, SUMINISTRO, ADQUISICIÓN, VENTA O DISTRIBUCIÓN DE PRODUCTOS FABRICADOS O DISTRIBUIDOS POR LA COMPAÑÍA; LA ADQUISICIÓN DE MATERIAS PRIMAS O MATERIALES Y EL DESCUENTO DE TÍTULOS- VALORES O DE CRÉDITOS ORIGINADOS DE LAS OPERACIONES SOCIALES; CREAR

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 10

LAS ACCIONES CON DERECHO A VOTO DE LA PERSONA EN CUESTIÓN SE CONSIDERA COMO EVENTO CONSTITUTIVO DE CONTROL SOBRE DICHA PERSONA.

(6) APROBAR O MODIFICAR O MODIFICAR EL PLAN ANUAL DE NEGOCIOS O EL PRESUPUESTO ANUAL DE LA COMPAÑÍA.

(7) REALIZAR ADQUISICIONES O INVERSIONES EN UNA O MAS CORPORACIONES, SOCIEDADES, ASOCIACIONES O CUALQUIER OTRA ORGANIZACIÓN O PERSONA JURÍDICA SIMILAR, POR UNA SUMA O SUMAS QUE, CONJUNTAMENTE, SUPEREN UN MONTO EQUIVALENTE A DOS MILLONES QUINIENTOS MIL DÓLARES (US\$2.500.000.00) DURANTE UN AÑO FISCAL.

L) AUTORIZAR AL REPRESENTANTE LEGAL PARA QUE SOLICITE, LLEGADO EL CASO, QUE SE ADMITA A LA COMPAÑÍA A LA CELEBRACIÓN DE CONCORDATO PREVENTIVO CON SUS ACREEDORES.

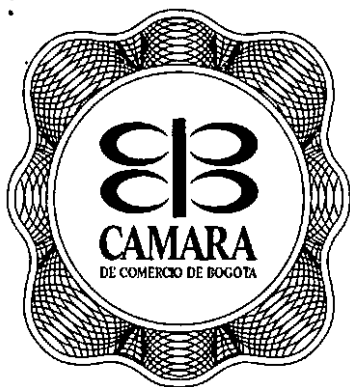
M) SERVIR DE ÓRGANO CONSULTIVO Y ASESOR DE LOS REPRESENTANTES DE LA COMPAÑÍA.

LA ADMINISTRACIÓN INMEDIATA DE LA COMPAÑÍA, SU REPRESENTACIÓN LEGAL Y LA GESTIÓN DE LOS NEGOCIOS SOCIALES ESTARÁN A CARGO DEL PRESIDENTE EJECUTIVO Y DE DOS (2) VICEPRESIDENTES EJECUTIVOS, DESIGNADOS POR LA JUNTA DIRECTIVA PARA PERIODOS DE UN AÑO, REELEGIBLES INDEFINIDAMENTE Y REMOVIBLES LIBREMENTE POR ELLA EN CUALQUIER TIEMPO, QUIENES COMO REPRESENTANTES LEGALES PODRÁN ACTUAR CONJUNTA O SEPARADAMENTE. TODOS LOS EMPLEADOS DE LA COMPAÑÍA CON EXCEPCIÓN DE LOS DESIGNADOS POR LA ASAMBLEA DE ACCIONISTAS Y LOS DEPENDIENTES DEL REVISOR FISCAL, SI LOS HUBIERE, ESTARÁN SOMETIDOS EN EL DESEMPEÑO DE SUS CARGOS A LOS REPRESENTANTES LEGALES.

LOS REPRESENTANTES LEGALES SON MANDATARIOS CON REPRESENTACIÓN INVESTIDOS DE FUNCIONES EJECUTIVAS Y ADMINISTRATIVAS Y COMO TALES TIENEN A SU CARGO LA REPRESENTACIÓN LEGAL DE LA COMPAÑÍA, LA GESTIÓN COMERCIAL Y FINANCIERA, LA RESPONSABILIDAD DE LA ACCIÓN ADMINISTRATIVA, LA COORDINACIÓN Y LA SUPERVISIÓN GENERAL DE LA EMPRESA, LAS CUALES CUMPLIRÁN CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS Y A LAS DISPOSICIONES LEGALES Y CON SUJECCIÓN A LAS ORDENES E INSTRUCCIONES DE LA JUNTA DIRECTIVA.

COMO REPRESENTANTES LEGALES DE LA COMPAÑÍA 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 CARÁCTER SIMPLEMENTE PREPARATORIO, ACCESORIO O COMPLEMENTARIO PARA LA REALIZACIÓN DE LOS FINES QUE PERSIGUE LA SOCIEDAD Y LOS

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46

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 11

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 COMPAÑÍA TENGA INTERÉS E INTERPONER TODOS LOS RECURSOS QUE SEAN PROCEDENTES CONFORME A LA LEY; DESISTIR DE LAS ACCIONES O RECURSOS QUE INTERPONGAN; NOVAR OBLIGACIONES O CRÉDITOS; DAR O RECIBIR BIENES EN PAGO; CONSTITUIR APODERADOS JUDICIALES O EXTRAJUDICIALES, DELEGARLES FACULTADES REVOCAR MANDATOS Y SUSTITUCIONES.

PARÁGRAFO: LOS REPRESENTANTES LEGALES DE LA SOCIEDAD TIENEN AMPLIAS FACULTADES, SIN NINGUNA LIMITACIÓN Y SIN REQUERIR AUTORIZACIÓN PREVIA DE LA JUNTA DIRECTIVA, PARA ACTUAR EN NOMBRE DE LA SOCIEDAD EN LICITACIONES PUBLICAS, PRIVADAS O CUALQUIER OTRA MODALIDAD DE CONTRATACIÓN, PRESENTAR PROPUESTAS, ACEPTAR ADJUDICACIONES Y CONTRATAR SIN LIMITACIÓN DE CUANTÍA ALGUNA ANTE LAS ENTIDADES PUBLICAS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMÍA MIXTA, BIEN SEAN ELLAS DEL ORDEN NACIONAL, DISTRITAL, DEPARTAMENTAL O MUNICIPAL.

CERTIFICA:

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

ORIGEN: JUNTA DIRECTIVA

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

FUE(RON) NOMBRADO(S):

PRESIDENTE EJECUTIVO

FRANCISCO JOSE BARBERI OSPINA

C.C.14445880

VICEPRESIDENTE EJECUTIVO

JUAN MANUEL BARBERI OSPINA

C.C.14949561

VICEPRESIDENTE EJECUTIVO

EMILIO SARDI APARICIO

C.C.14434582

CERTIFICA:

DOCUMENTO: ACTA No. 70 DEL 22 DE ENERO DE 2009

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 13 DE MARZO DE 2009 No. 2979 DEL LIBRO IX

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 12

DOCUMENTO: ACTA No. 74 DEL 15 DE OCTUBRE DE 2010

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 25 DE OCTUBRE DE 2010 No. 12493 DEL LIBRO IX

DOCUMENTO: ACTA No. 75 DEL 30 DE MARZO DE 2011

ORIGEN: ASAMBLEA GENERAL

INSCRIPCION: 04 DE MAYO DE 2011 No. 5355 DEL LIBRO IX

FUE(ON) _NOMBRADO(S)

JUNTA DIRECTIVA

PRINCIPALES

PRIMER RENGLON

FRANCISCO JOSE BARBERI OSPINA

C.C.14445880

SEGUNDO RENGLON

JUAN MANUEL BARBERI OSPINA

C.C.14949561

TERCER RENGLON

MAURICIO BARBERI BLUM

C.C.16749545

CUARTO RENGLON

SANTIAGO BARBERI GONZALEZ

C.C.94384742

QUINTO RENGLON

FRANCISCO PIEDRAHITA PLATA

C.C.14934246

SEXTO RENGLON

ISAAC YANOVICH FARBAIARZ

C.C.8243355

SEPTIMO RENGLON

ROBERTO ALBISETTI

PPTE.IFC94809

OCTAVO RENGLON

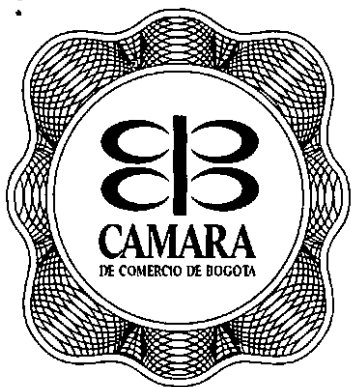
LUIS ERNESTO MEJIA CASTRO

C.C.16685633

NOVENO RENGLON

JAIME BERMUDEZ MERIZALDE

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46

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 13

C.C.79386262

SUPLENTES

PRIMER RENGLON

EMILIO SARDI APARICIO

C.C.14434582

SEGUNDO RENGLON

JORGE ENRIQUE ARIZA BERNAL

C.C.19494493

TERCER RENGLON

ANA MARIA ALVAREZ ROBLEDO

C.C.31170896

CUARTO RENGLON

MARIA TERESA CAÑON DE GUZMAN

C.C.31238104

QUINTO RENGLON

ANTONIO JAIRO RAMIREZ ECHAVE

C.C.16741040

SEXTO RENGLON

ALONSO BOTERO PARDO

C.C.16830282

SEPTIMO RENGLON

ANGELA MARIA FONSECA ARANGO

C.C.51902267

OCTAVO RENGLON

ERNESTO TRUJILLO PEREZ

C.C.14984104

NOVENO RENGLON

MARIA DEL PILAR CORREA LENIS

C.C.31931424

CERTIFICA:

DOCUMENTO: ACTA No. 59 DEL 31 DE MARZO DE 2003

ORIGEN: ASAMBLEA DE ACCIONISTAS

INSCRIPCION: 23 DE ABRIL DE 2003 No. 2845 DEL LIBRO IX

FUE(RON) NOMBRADO(S):

REVISOR FISCAL

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 14

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

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 26 DE AGOSTO DE 2004
ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA
INSCRIPCION: 30 DE AGOSTO DE 2004 No. 9417 DEL LIBRO IX
FUE(ON) NOMBRADO(S):
REVISOR FISCAL PRINCIPAL
LUIS FERNANDO QUICENO BENAVIDES
C.C.6106227

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 08 DE JUNIO DE 2009
ORIGEN: DELOITTE & TOUCHE LTDA D & T LTDA
INSCRIPCION: 11 DE JUNIO DE 2009 No. 6757 DEL LIBRO IX
FUE(ON) NOMBRADO(S):
REVISOR FISCAL SUPLENTE
KENELMA JUDITH PALENCIA CABANA
C.C.29181230

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,

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42

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 15

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 CEÑIRA 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.

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 BAUTISTA 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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

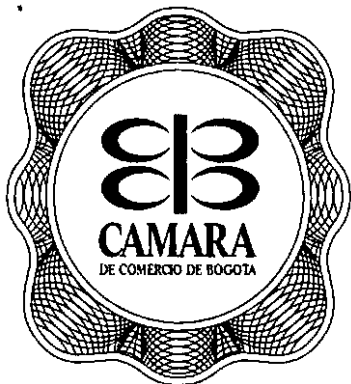
OPERACION: 02C261215120

PAGINA: 16

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 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.

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48

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 17

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 MARÍA ÁLVAREZ 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 LA DESIGNACIÓN DE APODERADOS.
 - F. ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACIÓN, DECLARACIONES DE PARTE Y RENDICIÓN DE TESTIMONIOS DENTRO DE LOS PROCESOS DE LA JURISDICCIÓN LABORAL Y TRÁMITES ADMINISTRATIVOS, CUANDO ELLO SEA REQUERIDO.
 - G. RESPONDER LAS DEMANDAS DE TUTELA DIRECTAMENTE O A TRAVÉS DE APODERADO ESPECIAL.
 - H. SUSCRIBIR LOS CONTRATOS DE TODO TIPO CON ENTIDADES EDUCATIVAS DE TODO ORDEN, SIN LIMITACIÓN DE CUANTÍA.
 - I. SUSCRIBIR LOS DOCUMENTOS Y ESCRITURAS DE DONACIÓN QUE SEAN AUTORIZADAS POR LA JUNTA DIRECTIVA, SIN LIMITACIÓN ALGUNA.
 - J. SUSCRIBIR TODOS LOS CONTRATOS DE CONSTRUCCIÓN, INSTALACIÓN, SERVICIOS,

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 18

REPARACIONES Y ADECUACIONES QUE SE REALICEN Y PRESTEN EN LA PLANTA Y SEDE ADMINISTRATIVA DE TECNOQUÍMICAS S.A. LOCALIZADAS EN CALI, HASTA POR LA SUMA EQUIVALENTE A TRESCIENTOS (300) SALARIOS MÍNIMOS LEGALES MENSUALES, DARLOS POR TERMINADO POR CUALQUIER CAUSA, PRESENTAR RECLAMOS ANTE LAS COMPAÑÍAS ASEGURADORAS, EXIGIR EL PAGO DE MULTAS E INDEMNIZACIONES DE CUALQUIER TIPO QUE ESTÉN 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 TRÁMITES QUE LA SOCIEDAD TECNOQUIMICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARÁCTER 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 FORMALIZACIÓN 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.

PARÁGRAFO I. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL, GUBERNATIVO, TRIBUNALES DE ARBITRAMIENTO Y RECLAMOS ANTE LAS COMPAÑÍAS ASEGURADORAS.

PARÁGRAFO II. LOS APODERADOS EJERCERÁN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACIÓN.

2. JORGE ENRIQUE ARIZA BERNAL, IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO. 19.494.493 DE BOGOTÁ, 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 TRÁMITES QUE LA SOCIEDAD TECNOQUÍMICAS S.A. REQUIERA ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

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49

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 19

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 TRÁMITES QUE LA SOCIEDAD TECNOQUÍMICAS S.A. REQUIERA

ADELANTAR ANTE LA ENTIDAD, ASÍ COMO DESIGNAR APODERADOS PARA INICIAR O RESPONDER PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

C. ANTE EL FONDO NACIONAL DE ESTUPEFACIENTES Y DIRECCIÓN 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 TRÁMITES QUE LA SOCIEDAD TECNOQUÍMICAS 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 CARÁCTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

D. EN TODO LO RELACIONADO CON LOS TRÁMITES DE IMPORTACIONES Y EXPORTACIONES, SEGÚN SE INDICA:

I. OTORGAR PODERES Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN ANTE LAS ADMINISTRACIONES DE ADUANAS DE LA DIRECCIÓN DE IMPUESTOS Y ADUANAS - DIAN - ASÍ COMO RENDIR DECLARACIONES, ATENDER VISITAS E INSPECCIONES Y FIRMAS 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, ASÍ COMO RESPONDER Y ATENDER LOS TRÁMITES DIRECTAMENTE O A TRAVÉS DE APODERADOS.

III- OTORGAR PODERES ESPECIALES Y GENERALES, OTORGAR GARANTÍAS 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 INTERMEDIACIÓN ADUANERA - SIA- Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE SE PRESENTEN Y TRAMITEN DE ACUERDA CON LA NORMATIVIDAD LEGAL SOBRE LA MATERIA.

V. SUSCRIBIR LAS CARTAS DE ANTINARCÓTICOS QUE SE PRESENTAN ANTE LA POLICÍA AEROPORTUARIA BIEN DIRECTAMENTE O AUTORIZANDO A LOS JEFES DE BODEGA DE YUMBO Y JAMUNDÍ PARA ESE TRÁMITE DOCUMENTOS DENTRO DE LOS TRÁMITES DE EXPORTACIONES O

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 20

REEMBARQUES DE MERCANCÍAS, Y EN GENERAL ATENDER TODAS LAS DILIGENCIAS DIRECTAMENTE U OTORGAR PODER AUN TERCERO.

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

E. SUSCRIBIR CONTRATOS, SIN LIMITACIÓN DE CUANTÍA QUE TENGA QUE VER CON LA ADQUISICIÓN DE EQUIPO Y MAQUINARIA, REPARACIÓN, ADECUACIÓN, INSTALACIÓN, SERVICIOS TÉCNICOS Y DE ASESORÍA.

E. SUSCRIBIR CONTRATOS DE FABRICACIÓN CON TERCEROS BIEN SEA QUE TECNOQUÍMICAS OBRE COMO FABRICANTE O COMO PROPIETARIO.

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

3. MARÍA TERESA CAÑÓN DE GUZMAN, IDENTIFICADA CON LA CÉDULA DE CIUDADANÍA NO. 31.238.104 DE CALI, CARLOS ARTURO PEÑA NIETO IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO. 19.483.439 DE BOGOTÁ Y ÁNGELA MARÍA CORREA CARDONA IDENTIFICADA CON LA CÉDULA DE CIUDADANÍA 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 TECNOQUÍMICAS S.A. EN:

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

LOS APODERADOS SUSCRIBIRÁN 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 PERSONERÍA A NOMBRE DE TECNOQUÍMICAS S.A., BIEN SEA DIRECTAMENTE O A TRAVÉS DE APODERADO, SIEMPRE QUE LO ESTIMEN CONVENIENTE, DE MANERA QUE EN

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 21

NINGÚN CASO QUEDE SIN LA DEBIDA REPRESENTACIÓN EN LA SALVAGUARDIA DE SUS DERECHOS Y CUMPLIMIENTO DE OBLIGACIONES DE CARÁCTER CAMBIARIO Y EN LOS ASUNTOS CONCERNIENTES PARA LAS MATERIAS DE QUE TRATA ESTE PODER.

B. EN RELACIÓN CON SECTOR FINANCIERO:

I. SUSCRIBIR LOS CONTRATOS DE CRÉDITO Y LEASING CON LOS BANCOS, ENTIDADES FINANCIERAS, COMPAÑÍAS DE FINANCIAMIENTO COMERCIAL, DE ACUERDO CON LOS CUPOS FIJADOS POR LA JUNTA DIRECTIVA, ASÍ COMO LOS PAGARÉS, LOS CONTRATOS DE GARANTÍA PRENDARIA E HIPOTECARIA, LA CONFIRMACIÓN DE FORWARDS Y TODOS LOS DEMÁS DOCUMENTOS QUE SEAN REQUERIDOS PARA LA CULMINACIÓN Y FORMALIZACIÓN DE ESTOS TRÁMITES.

ESTAS FACULTADES IGUALMENTE APLICAN PARA TODOS LOS CRÉDITOS 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 ELECTRÓNICA Y LOS FORMULADOS ÚNICOS DE CONOCIMIENTO DE PERSONA JURÍDICA QUE EXIGE EL SECTOR FINANCIERO.

III. SUSCRIBIR LAS LETRAS DE COBRANZA Y LAS CARTAS DE CRÉDITO.

C. SOLICITAR TIDIS Y FIRMAR TODOS LOS DOCUMENTOS RELACIONADOS CON ESTE TRÁMITE.

D. EN RELACIÓN CON LA COMPAÑÍAS ASEGURADORAS:

I. SUSCRIBIR DOCUMENTOS DE RECLAMACIÓN Y OTORGAR PODERES PARA QUE COMPAREZCAN A LAS AUDIENCIAS DE RECLAMACIONES, ASÍ COMO LOS DOCUMENTOS DE TRANSACCIÓN. ESTAS FACULTADES SE OTORGAN SIN LIMITACIÓN DE CUANTÍA.

II. SUSCRIBIR LAS CARTAS DE NO RECLAMACIÓN A LAS COMPAÑÍAS ASEGURADORAS POR OCURRENCIA DE SINIESTROS Y LAS RESPECTIVAS CONSTANCIAS.

III. SUSCRIBIR LOS DOCUMENTOS REQUERIDOS POR EL SISTEMA DE INFORMACIÓN PARA LA PREVENCIÓN DE LAVADO DE ACTIVOS (SIPLA).

E. FORMULAR PETICIONES RELACIONADAS CON LAS FACULTADES OTORGADAS.

PARÁGRAFO 1. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O GUBERNATIVO.

PARÁGRAFO II. LOS APODERADOS EJERCERÁN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACIÓN.

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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 22

A. OTORGAR PODER Y CONSTITUIR MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACIÓN DE LA CARTERA, SIN LIMITACION DE CUANTÍA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACIÓN, CON AUTORIZACIÓN 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 TECNOQUÍMICAS S. A.

B. SUSCRIBIR LOS CONTRATOS DE ARRENDAMIENTO DE INMUEBLES, SU MODIFICACIÓN Y O TERMINACIÓN, INVENTARIOS Y ANEXOS PERTINENTES, BIEN SEA QUE LA SOCIEDAD OBRE COMO ARRENDADOR O ARRENDATARIO, SIN LIMITACIÓN DE CUANTÍA. ESTA FUNCIÓN LA PODRÁ EJERCER DIRECTAMENTE O MEDIANTE LA DESIGNACIÓN DE APODERADOS.

C. SUSCRIBIR LOS FORMATOS DE AUTORIZACIÓN DE CREACIÓN DE CLIENTES Y PROVEEDORES DE LA EMPRESA.

D. EN RELACIÓN CON LOS VEHÍCULOS DE TODO TIPO QUE FIGUREN A NOMBRE DE TECNOQUÍMICAS, 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 VEHÍCULOS.

PARÁGRAFO. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL O ADMINISTRATIVO DE CUALQUIER ORDEN.

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

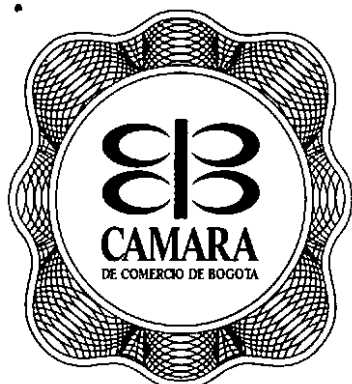
CERTIFICA:

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

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51

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 23

FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.

- ESPERANZA GRANADOS JAIMES, C.C. 63.392.189 DE MALAGA (SANTANDER), SUBGERENTE ADMINISTRATIVO DE LA REGIONAL CUNDINAMARCA DE LA SOCIEDAD, CON SEDE EN BOGOTA D.C.

- DIEGO FERNANDO MUÑOZ QUINTERO, C.C. 94.282.452 DE CALI, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ANTIOQUIA DE LA SOCIEDAD, CON SEDE EN MEDELLIN.

- CARLOS ORLANDO MUTIS PICON, C.C. 91.200.418 DE BUCARAMANGA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ORIENTE DE LA SOCIEDAD, CON SEDE EN BUCARAMANGA.

- DANIEL AMEZQUITA LIZARAZO, C.C. 8.681.962 DE BARRANQUILLA, SUBGERENTE FINANCIERO Y ADMINISTRATIVO DE LA REGIONAL ATLANTICO DE LA SOCIEDAD, CON SEDE EN BARRANQUILLA.

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

1.PARA QUE EN NOMBRE DE TECNOQUIMICAS S.A., Y EN ASUNTOS QUE TENGA QUE VER CON SUS RESPECTIVOS DISTRITOS DE VENTAS SE NOTIFIQUEN Y PROMUEVAN ACCIONES EN NOMBRE DE ESTA ANTE ENTIDADES PUBLICAS, FUNCIONARIOS O EMPLEADOS NACIONALES, DEPARTAMENTALES, DISTRITALES Y MUNICIPALES DEL ORDEN JUDICIAL, ADMINISTRATIVO POLICIVO, PENAL O DE FISCALIA, YA SEA EN PROCESOS, ACTUACIONES, SIMPLES ACTOS O DILIGENCIAS Y GESTIONES, CON FACULTADES DE DESISTIMIENTO, ALLANAMIENTO Y CONCILIACION, EN LOS QUE EL ESTABLECIMIENTO ESTE VINCULADO COMO DEMANDANTE, DEMANDADO O TERCERO INTERVINIENTE.

PARAGRAFO: LA FACULTAD DE CONCILIACION, DESISTIMIENTO Y ALLANAMIENTO SE LIMITA HASTA LA SUMA EQUIVALENTE A CINCUENTA (50) SALARIOS MINIMOS LEGALES MENSUALES.

2.PARA QUE OTORGUEN PODERES Y CONSTITUYAN MANDATARIOS PARA INICIAR LAS ACCIONES CIVILES, COMERCIALES Y PENALES TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A LAS AUDIENCIAS DE CONCILIACION E INTERROGATORIOS DE PARTE, CON AUTORIZACION PARA TRANSIGIR, DESISTIR, CONCILIAR O COMPROMETER A LA SOCIEDAD EN TODOS LOS PROCESOS, GESTIONES JUDICIALES, ADMINISTRATIVOS O RECLAMACIONES EXTRA PROCESO EN QUE INTERVENGA EN ASUNTOS RELACIONADOS CON EL ESTABLECIMIENTO DE COMERCIO, CON LAS LIMITACIONES PREVISTAS EN EL PARAGRAFO

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 24

DEL NUMERAL ANTERIOR.

3.PARA QUE OTORQUE PODERES Y CONSTITUYAN MANDATARIOS PARA HACERSE PARTE EN LOS PROCESOS CONCORDATARIOS, DE LIQUIDACION OBLIGATORIA, O REESTRUCTURACION ECONOMICA QUE SE TRAMITEN ANTE LA SUPERINTENDENCIA DE SOCIEDADES O ANTE OTRAS SUPERINTENDENCIAS O ENTIDADES CUANDO SE TRATE DE OTRA CLASE DE DEUDORES, TENDIENTES A LA RECUPERACION DE LA CARTERA, SIN LIMITACION DE CUANTIA, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE LA SOCIEDAD A 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.

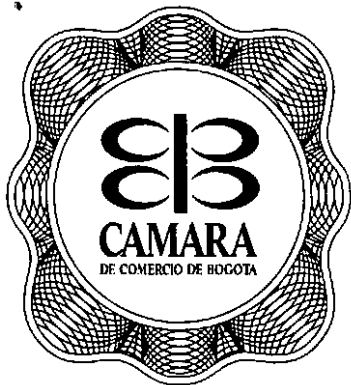
6.SUSCRIBIR LOS CONTRATOS DE PRENDA SOBRE VEHICULOS DE PROPIEDAD DE TERCEROS PARA RESPALDAR LOS PRESTAMOS QUE LA EMPRESA OTORQUE Y TODO LOS DOCUMENTOS QUE SEAN REQUERIDOS PARA SU FORMALIZACION ANTE LAS SECRETARIAS DE TRANSITO Y/O MOVILIDAD DE LOS RESPECTIVOS MUNICIPIOS. ESTE PODER TAMBIEN COMPRENDE LA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

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:

QUE POR ESCRITURA NRO. 2687 DEL 26 DE JUNIO DE 2009 NOTARIA TERCERA DE CALI ,

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52

CERTIFICADO NACIONAL

OPERACION: 02C261215120

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 26

27037 DEL CONSEJO SUPERIOR DE LA JUDICATURA, PARA QUE DE MANERA CONJUNTA O SEPARADA EJERZAN LAS SIGUIENTES FACULTADES EN NOMBRE DE TECNOQUÍMICAS SA.:

1. NOTIFICARSE, CONTESTAR DEMANDAS O REQUERIMIENTOS, CONCILIAR, DESISTIR, ALLANARSE EN CUALQUIER PROCESO JUDICIAL, ADMINISTRATIVO O GUBERNATIVO, SIN IMPORTAR LA CUANTIA NI LA NATURALEZA DE LA ACCIÓN, QUE SE LE FORMULE A TECNOQUÍMICAS, BIEN SEA POR PERSONA NATURAL, JURÍDICA, EMPRESA INDUSTRIAL Y COMERCIAL DEL ESTADO, ESTABLECIMIENTOS PÚBLICOS Y/O ENTIDADES GUBERNATIVAS DE CUALQUIER ORDEN, EN LA QUE LA EMPRESA TENGA INTERÉS COMO ACTOR, DEMANDADO, TERCERO INTERVINIENTE O LLAMADO EN GARANTÍA Y/O EN CUALQUIER MODALIDAD PROCESAL EN QUE SEA VINCULADA.

2. ASISTIR A LAS AUDIENCIAS DE CONCILIACIÓN EN LA QUE SEA CONVOCADA LA EMPRESA COMO PARTE DEMANDANTE O DEMANDADA, CON PLENAS FACULTADES PARA CONCILIAR, DESISTIR, ALLANARSE Y COMPROMETER.

3. REPRESENTAR A LA SOCIEDAD PARA ATENDER LAS DILIGENCIAS DE DECLARACIÓN DE PARTE EN CUALQUIER PROCESO JUDICIAL O TRÁMITE GUBERNATIVO AL QUE SEAN CONVOCADO EL REPRESENTANTE LEGAL DE LA SOCIEDAD.

4. INICIAR TODA CLASE DE PROCESOS Y TRÁMITES ANTE LA AUTORIDADES JUDICIALES O GUBERNATIVAS EN LA QUE LA SOCIEDAD TENGA INTERÉS.

PARAGRAFO: PARA EL EJERCICIO DE LAS FACULTADES PREVISTAS EN LOS NUMERALES 1 Y 4 PODRÁN OTORGAR PODER A TERCEROS PARA LA ATENCIÓN DE LOS ASUNTOS MENCIONADOS.

TERCERO. LA ACEPTACIÓN DE LA GESTIÓN POR PARTE DE ANTONIO JAIRO RAMÍREZ ECHAVE, ANA MARÍA ALVAREZ Y RODRIGO VELÁSQUEZ LÓPEZ SE ENTENDERÁ PRESTADA CON EL EJERCICIO DE LAS FACULTADES CONFERIDAS Y/O LA SUSCRIPCIÓN DE LOS DOCUMENTOS.

ESTE MANDATO SE OTORGA POR TERMINO INDEFINIDO.

COMPARECEN ANTONIO JAIRO RAMIREZ ECHAVE CON DOMICILIO Y RESIDENCIA EN LA CIUDAD DE CALI, IDENTIFICADO CON LA C.C. NO. 16.741.040 DE CALI, ANA MARÍA ALVAREZ ROBLEDO CON C.C. 31.170.896 DE CALI Y RODRIGO VELASQUEZ LOPEZ, CON C. C. 16.589.361 DE CALI, Y MANIFIESTAN QUE ACEPTAN EL PODER GENERAL QUE SE LES CONFIERE POR ÉSTE INSTRUMENTO.

CERTIFICA:

QUE POR ESCRITURA NRO. 4765 DEL 16 DE NOVIEMBRE DE 2010 NOTARIA TERCERA DE CALI, INSCRITA EN LA CAMARA DE COMERCIO EL 03 DE DICIEMBRE DE 2010 BAJO EL NRO. 144 DEL LIBRO V MEDIANTE LA CUAL SE CONCEDE PODER ESPECIAL, AMPLIO Y

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 28

SOLICITUDES, ACLARACIONES, RESPUESTAS A REQUERIMIENTOS, SOLICITUD DE CONCEPTOS Y EN GENERAL CUALQUIER TRAMITE QUE SEA NECESARIO ADELANTAR ANTE ESTA ENTIDAD O LA QUE HAGA SUS VECES. C) FONDO NACIONAL DE ESTUPEFACIENTES, INCLUIDO PERO SIN LIMITARSE A LOS TRAMITES NECESARIOS PARA LA APROBACION DE COMPRA DE MEDICAMENTOS Y MATERIAS PRIMAS DE CONTROL ESPECIAL, ELEVAR SOLICITUDES DE CORRECCION DE RESOLUCIONES, DESISTIMIENTOS, ACLARACIONES, RESPUESTAS A REQUERIMIENTOS, SOLICITUD DE CONCEPTOS Y EN GENERAL CUALQUIER TRAMITE QUE SEA NECESARIO ADELANTAR ANTE ESTA ENTIDAD O LA QUE HAGA SUS VECES. D) EMPRESA TERRITORIAL PARA LA SALUD. ETESA, INCLUIDO PERO SIN LIMITARSE A LA SOLICITUD DE NO OBJECCION PARA LA REALIZACION DE ACTIVIDADES PROMOCIONALES CONSISTENTES EN JUEGOS DE SUERTE Y AZAR QUE REALICE LA COMPAÑIA CON EL FIN DE IMPULSAR SUS VENTAS, RESPONDER REQUERIMIENTOS, HACER ACLARACIONES, PRESENTAR RECURSOS, SOLICITAR CONCEPTOS Y EN GENERAL CUALQUIER TRAMITE Y SOLICITUD QUE SEA NECESARIO ADELANTAR ANTE ESTA ENTIDAD O LA QUE HAGA SUS VECES. E) INSTITUTO COLOMBIANO AGROPECUARIO Y MINISTERIO DE MEDIO AMBIENTE, INCLUIDO PERO SIN LIMITARSE A LA SOLICITUD DE LICENCIAS AUTORIZACIONES PARA IMPORTAR Y EXPORTAR, OBTENCION DE REGISTROS, SOLICITUD DE CONCEPTOS, CONTESTAR REQUERIMIENTOS, PRESENTAR DECLARACIONES, SUMINISTRAR INFORMACION REQUERIDA, SOLICITAR CONCEPTOS Y EN GENERAL CUALQUIER TRAMITE Y SOLICITUD QUE SEA NECESARIO ADELANTAR ANTE ESTA ENTIDAD O LA QUE HAGA SUS VECES. F) MINISTERIO DE PROTECCION SOCIAL, SECRETARIAS DE SALUD E INSTITUTO NACIONAL DE SALUD, INCLUIDO PERO SIN LIMITARSE A LA PRESENTACION DE CUALQUIER SOLICITUD DE APERTURA DE INVESTIGACION, SOLICITUD CONCEPTO, RESPONDER REQUERIMIENTOS POR QUEJAS O INVESTIGACIONES Y DEMAS SOLICITUDES Y TRAMITES QUE DEBAN ADELANTARSE ANTE ESTAS ENTIDADES O LAS QUE HAGAN SUS VECES. G) CUALQUIER ENTIDAD DEL ORDEN NACIONAL, LOCAL O MUNICIPAL, QUE HAGA REQUERIMIENTOS O SOLICITE ACLARACIONES A LA COMPAÑIA EN EL CURSO DE CUALQUIER TIPO DE TRAMITE ADMINISTRATIVO, PARA LO CUAL LOS APODERADOS QUEDAN DEBIDAMENTE FACULTADOS PARA CONTESTAR Y ACLARAR Y SOLICITAR TODO CUANTO SEA DEBIDO. PARA EFECTOS DE TODO LO ANTERIOR, FACULTO A LOS APODERADOS AQUI NOMBRADOS, APRA DAR ANTE DICHAS AUTORIDADES TODOS LOS PASOS NECESARIOS, PRESENTAR SOLICITUDES, HACER DECLARACIONES, PAGAR DERECHOS, PROBAR EXPLOTACIONES, SOLICITAR TESTIMONIOS, RECIBIR DOCUMENTOS, FORMULAR TODOS LOS RECURSOS, QUE SEAN PROCEDENTES, PETICIONES, RECLAMOS CON ATRIBUCIONES PARA DESISTIR Y CONCILIAR, OTORGAR PODERES, SUSTITUIRLOS Y REASUMIRLOS. ASI MISMO, LOS APODERADOS ESTAN AUTORIZADOS PARA HACER CUANTO

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54

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 29

FUERE NECESARIO ANTE LAS AUTORIDADES ADMINISTRATIVAS PARA LOS FINES ARRIBA INDICADOS CON TODAS LAS DEMAS FACULTADES GENERALES Y ESPECIALES QUE FUEREN NECESARIAS, PUDIENDO ATENDER ASI MISMO LAS NOTIFICACIONES QUE DIRECTA O INDIRECTAMENTE SE GENEREN DE LOS ACTOS, ACTUACIONES, DILIGENCIAS O GESTIONES QUE TENGAN RELACION DE CAUSALIDAD POR LOS SUSODICHOS TRAMITES. LA ACEPTACION DE LA GESETION POR PARTE DE ANTONIO JAIRO RAMIREZ ECHAVE, BEATRIZ EUGENIA TORRES HURTADO, ADRIANA MARIA MORALES JIMENEZ Y JUAN CAMILO CARDONA MELO SE ENTENDERA PRESTADA CON EL DOCUMENTO EN QUE SOLICITEN CADA TRAMITE ANTE LA ENTIDAD RESPECTIVA. ESTE MANDATO SE OTORGA POR TERMINO INDEFINIDO Y REVOKA LA ESCRITURA NO. 1853 DEL 7 DE MAYO DE 2009.

CERTIFICA:

QUE POR ESCRITURA NRO. 4974 DEL 26 DE NOVIEMBRE DE 2010 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 10 DE DICIEMBRE DE 2010 BAJO EL NRO. 150 DEL LIBRO V , SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE E INDISTINTAMENTE, A JUAN CAMILO CARDONA MELO, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA No.1130666199 DE CALI Y PORTADOR DE LA TARJETA PROFESIONAL DE ABOGADO No.193140 DEL CONSEJO SUPERIOR DE LA JUDICATURA, Y/O A ADRIANA MARIA MORALES JIMENEZ, MAYOR DE EDAD, VECINA DE ESTA CIUDAD, IDENTIFICADA CON CÉDULA DE CIUDADANÍA No. 67024965 DE CALI Y PORTADORA DE LA TARJETA PROFESIONAL DE ABOGADA No.193141 DEL C.S. DE LA J., PARA QUE CONJUNTAMENTE O POR SEPARADO, EN NOMBRE Y REPRESENTACIÓN DE LA SOCIEDAD, CUYA PERSONERÍA OSTENTA: 1o.) PROMUEVAN O DESISTAN DE ACCIONES ANTE CORPORACIONES, ENTIDADES O FUNCIONARIOS DEL ORDEN JUDICIAL, ADMINISTRATIVO O GUBERNATIVO, YA SEA EN TRÁMITES O PROCESOS, ACTUACIONES O ACTOS SIMPLES, ENTRE ELLAS ACCIONES DE TUTELA, INCIDENTES, DILIGENCIAS O GESTIONES EN QUE TECNOQUÍMICAS S.A. TENGA INTERÉS COMO ACTOR, DEMANDANDO O TERCERO INTERVINIENTE EN RELACIÓN CON LOS ASUNTOS DE CARÁCTER LABORAL, POLICIVO, PENAL O DE FISCALÍA, EN QUE LA EMPRESA SEA PARTE ACTIVA O PASIVA, CON CAPACIDAD PARA NOTIFICARSE Y CONTESTAR Y HACERSE PARTE EN ELLOS EN NOMBRE DE TECNOQUÍMICAS S. A. 2o.) CONSTITUYAN APODERADOS EN DESARROLLO DE ESTA REPRESENTACIÓN LABORAL, REVOQUEN Y SUSTITUYAN DICHOS PODERES CUANDO LO ESTIMEN PROCEDENTE. 3o.) TRANSIJAN, CONCILIE, DESISTAN Y COMPROMETAN A LA EMPRESA EN TODOS LOS TRAMITES ADMINISTRATIVOS Y PROCESOS JUDICIALES, DE CARÁCTER LABORAL, POLICIVO, PENAL O DE FISCALÍA EN LOS QUE LA EMPRESA SEA PARTE DEMANDANTE, DEMANDADA O TERCERO INTERVINIENTE. PARÁGRAFO. LA FACULTAD PARA TRANSIGIR O CONCILIAR SE

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

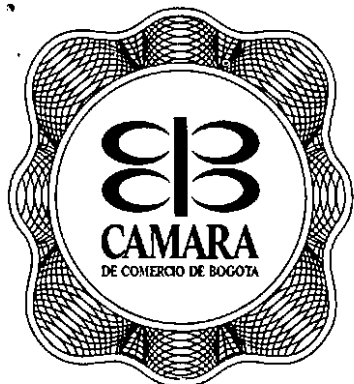
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OPERACION: 02C261215120

PAGINA: 30

LIMITA A LA SUMA DE QUINIENTOS (500) SALARIOS LEGALES MENSUALES. 4o.) OTORGUEN PODERES Y CONSTITUYAN MANDATARIOS PARA INICIAR LAS ACCIONES JUDICIALES DE CARÁCTER CIVIL, COMERCIAL Y PENAL TENDIENTES A LA RECUPERACIÓN DE LOS CRÉDITOS A FAVOR DE LA SOCIEDAD, BIEN SEA REPRESENTADOS EN FACTURAS, CHEQUES, TÍTULOS VALORES O CUALQUIER OTRO DOCUMENTO REPRESENTATIVO DE CRÉDITO, HASTA POR SUMA EQUIVALENTE A QUINIENTOS (500) SALARIOS MÍNIMOS LEGALES MENSUALES, CON EXPRESAS FACULTADES PARA ASISTIR EN NOMBRE DE TECNOQUÍMICAS S.A. A LAS AUDIENCIAS DE CONCILIACIÓN QUE PROGRAMEN LOS JUZGADOS CIVILES MUNICIPALES Y DEL CIRCUITO, CON AUTORIZACIÓN PARA TRANSIGIR, DESISTIR CONCILIAR O COMPROMETER A LA SOCIEDAD HASTA POR LA CUANTÍA INDICADA. 5o. REPRESENTEN A TECNOQUÍMICAS S.A. DENTRO DE LOS TRÁMITES DE CONCORDATOS, PROCESOS DE REESTRUCTURACIÓN ECONÓMICA PREVISTO EN LA LEY 550 DE 1999, Y MODIFICADOS POR EL RÉGIMEN DE INSOLVENCIA EMPRESARIAL Y DE PERSONA NATURAL NO COMERCIANTE, REGULADAS EN LAS LEYES 1116 DE 2006 Y 1380 DE 2010 Y LAS DEMÁS NORMAS QUE LAS ADICIONEN O MODIFIQUEN, O QUE LLEGAREN A REGULAR LOS PROCEDIMIENTOS DE INSOLVENCIA O ILIQUIDEZ DE PERSONAS NATURALES O JURÍDICAS, ASÍ COMO LAS 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 CRÉDITOS, 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 CRÉDITOS PRESENTADOS. LAS FACULTADES AQUÍ ESTABLECIDAS ESTÁN LIMITADAS PARA LOS CRÉDITOS HASTA POR CUANTÍA DE QUINIENTOS (500) SALARIOS MÍNIMOS LEGALES MENSUALES. PARÁGRAFO. IGUALMENTE QUEDAN FACULTADOS PARA ACEPTAR Y REPRESENTAR A TECNOQUÍMICAS CUANDO LA EMPRESA SEA NOMBRADA EN JUNTA DE ACREEDORES O EN ÓRGANOS 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. 6o.) REPRESENTEN A TECNOQUÍMICAS S.A. EN LOS PROCEDIMIENTOS DE CONCILIACIÓN 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

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 31

MÍNIMOS LEGALES MENSUALES. 7o.) REVISEN LOS EXPEDIENTES DE LOS PROCESOS JUDICIALES DE CARÁCTER EJECUTIVO EN QUE LA SOCIEDAD SEA PARTE DEMANDANTE, EN TODO EL TERRITORIO NACIONAL, PARA LA RECUPERACIÓN DE SUS ACREENCIAS. 8o.) APRUEBEN Y SUSCRIBAN ACUERDOS PRIVADOS DE PAGO Y CONCILIACIONES DE OBLIGACIONES A FAVOR DE TECNOQUÍMICAS POR LA VENTA DE SUS PRODUCTOS HASTA POR LA SUMA DE (500) SALARIOS MÍNIMOS LEGALES MENSUALES.

CADA UNO DE LOS APODERADOS AQUÍ MENCIONADOS, SE CEÑIRÁ RIGUROSAMENTE A LOS TÉRMINOS EXPRESADOS EN ESTE MANDATO QUE SE OTORGA POR TÉRMINO INDEFINIDO Y CUALQUIER MODIFICACIÓN O REVOCATORIA SE HARÁ EXPRESAMENTE POR ESCRITURA PÚBLICA.

CERTIFICA:

QUE POR ESCRITURA NRO. 2755 DEL 19 DE JULIO DE 2011 NOTARIA TERCERA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 28 DE JULIO DE 2011 BAJO EL NRO. 100 DEL LIBRO V MEDIANTE LA CUAL SE LE CONCEDE PODER ESPECIAL, AMPLIO Y SUFICIENTE A CARLOS ALBERTO QUINTERO ROA, MAYOR DE EDAD, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA NO. 14.440.778 DE CALI, PARA QUE EN NOMBRE Y REPRESENTACIÓN DE TECNOQUÍMICAS S.A., CUYA PERSONERÍA OSTENTA, LA REPRESENTE EN LOS SIGUIENTES ACTOS: A) PRESENTAR EN LA ADMINISTRACIÓN DE IMPUESTOS Y ADUANAS NACIONALES - DIAN- O DEL ORGANISMO QUE HAGA SUS VECES, Y FIRMAR EN REPRESENTACIÓN DE LA SOCIEDAD LAS DECLARACIONES DEL IMPUESTO SOBRE LA RENTA Y COMPLEMENTARIOS A CARGO DE LA SOCIEDAD Y TODAS LAS DEMÁS DECLARACIONES QUE DEBA PRESENTAR ANTE DICHA ENTIDAD, TALES COMO LA DE VENTAS, RETENCIÓN EN LA FUENTE, Y CUALQUIERA OTRA DECLARACIÓN QUE POR LEY ESTÉ OBLIGADA A PRESENTAR. B) NOTIFICARSE EN REPRESENTACIÓN DE LA SOCIEDAD, DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES QUE EXPIDA O REALICE LA ADMINISTRACIÓN DE IMPUESTOS Y ADUANAS NACIONALES - DIAN- O DEL ORGANISMO QUE HAGA SUS VECES, EN RELACIÓN CON TODOS TRIBUTOS Y OBLIGACIONES FORMALES Y/O SUSTANCIALES QUE SEAN ADMINISTRADAS POR ESA ENTIDAD.

C) PRESENTAR Y SUSCRIBIR TODOS LOS DOCUMENTOS QUE OBLIGUEN A LA SOCIEDAD COMO DECLARANTE DEL IMPUESTO DE INDUSTRIA Y COMERCIO Y EL COMPLEMENTARIO DE AVISOS Y TABLEROS EN EL MUNICIPIO EN QUE LA SOCIEDAD ESTÉ OBLIGADA AL PAGO DE LOS CITADOS IMPUESTOS, ASÍ COMO TODOS LOS DOCUMENTOS QUE OBLIGUEN AL PAGO DE OTROS TRIBUTOS DE CARÁCTER TERRITORIAL ANTE LOS MUNICIPIOS EN QUE ESTOS SE CAUSEN.

D) NOTIFICARSE EN REPRESENTACIÓN DE LA SOCIEDAD, DE TODAS LAS ACTUACIONES, ACTOS, DILIGENCIAS O GESTIONES QUE EXPIDAN O REALICEN LOS MUNICIPIOS Y

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 32

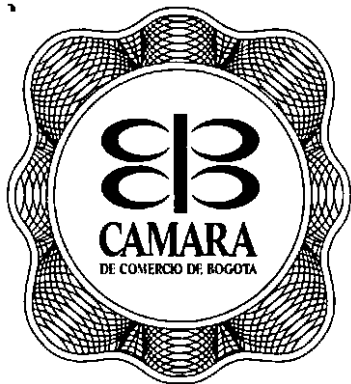
DEPARTAMENTOS, EN RELACIÓN CON TODOS TRIBUTOS Y OBLIGACIONES FORMALES Y/O SUSTANCIALES QUE SEAN ADMINISTRADAS POR ESTAS ENTIDADES. E) RESPONDER EN REPRESENTACIÓN DE LA SOCIEDAD TODO TIPO DE EMPLAZAMIENTOS, REQUERIMIENTOS ORDINARIOS Y ESPECIALES, PLIEGO DE CARGOS, SOLICITUDES DE INFORMACIÓN Y DEMÁS ACTOS ADMINISTRATIVOS EN RELACIÓN CON TODOS LOS TRIBUTOS Y OBLIGACIONES FORMALES Y/O SUSTANCIALES ADMINISTRADAS POR LA DIRECCIÓN DE IMPUESTOS Y ADUANAS NACIONALES, DIAN, O POR LA ENTIDAD QUE ASUMA Y DESARROLLE ESAS FUNCIONES Y POR LAS DEPENDENCIAS MUNICIPALES, DEPARTAMENTALES Y DISTRITALES QUE ADMINISTREN LOS TRIBUTOS Y OBLIGACIONES FORMALES Y/O SUSTANCIALES DE CARÁCTER TERRITORIAL. F) INTERPONER, SUBSANAR Y DESISTIR EN REPRESENTACIÓN DE LA SOCIEDAD DE LOS RECURSOS EN LA VÍA GUBERNATIVA QUE SEAN PROCEDENTES DE ACUERDO CON LA LEY, CONTRA LAS LIQUIDACIONES OFICIALES DE REVISIÓN, AFORO Y CORRECCIÓN ARITMÉTICA, RESOLUCIÓN SANCIÓN Y CONTRA TODO TIPO DE ACTOS ADMINISTRATIVOS QUE PROFIERA LA ADMINISTRACIÓN DE IMPUESTOS NACIONALES -DIAN- Y LAS ENTIDADES TERRITORIALES EN RELACIÓN CON TODOS LOS TRIBUTOS Y OBLIGACIONES FORMALES Y/O SUSTANCIALES QUE ADMINISTREN Y/O RECAUDEN. G) EN GENERAL, PARA QUE ASUMA LA PERSONERÍA EN NOMBRE DE LA SOCIEDAD SIEMPRE QUE LO ESTIME CONVENIENTE, DE MANERA QUE EN NINGÚN CASO QUEDE SIN REPRESENTACIÓN EN LOS ASUNTOS RELACIONADOS CON LAS FACULTADES OTORGADAS. PARÁGRAFO 1. EN LA ATENCIÓN DE TODOS LOS ASUNTOS MENCIONADOS TENDRÁ LA FACULTAD DE DESIGNAR APODERADOS PARA INICIAR, RESPONDER REQUERIMIENTOS O DEMANDAS, O HACERSE PARTE EN PROCESOS DE CARÁCTER JUDICIAL, GUBERNATIVO, TRIBUNALES DE ARBITRAMIENTO Y RECLAMOS ANTE LAS COMPAÑÍAS ASEGURADORAS. PARÁGRAFO II. LOS APODERADOS QUE DESIGNE EL SEÑOR QUINTERO EJERCERÁN SUS FUNCIONES DE MANERA INDIVIDUAL Y SIN ORDEN DE PRELACIÓN. ESTE PODER ESTARÁ VIGENTE HASTA TANTO SEA REVOCADO O MODIFICADO EXPRESAMENTE POR ESCRITURA PÚBLICA. TERCERO: CON EL OTORGAMIENTO DE ESTE PODER SE REVOKA EL OTORGADO MEDIANTE ESCRITURA PÚBLICA NO. 5235 DEL 19 DE JULIO DE 1996, DE LA NOTARÍA DÉCIMA DE CALI, REGISTRADO EN LA CÁMARA DE COMERCIO DE CALI EL 25 DE JULIO DEL MISMO AÑO BAJO EL NO. 144 DEL LIBRO V. PRESENTE CARLOS ALBERTO QUINTERO ROA, VECINO DE ESTA CIUDAD, IDENTIFICADO CON LA CÉDULA DE CIUDADANÍA 14.440.778 DE CALI, MANIFIESTA QUE ACEPTA EL PODER QUE POR ESTA ESCRITURA LE CONFIERE LA SOCIEDAD TECNOQUÍMICAS S.A.

CERTIFICA:

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

NUMERO DE ACCIONES: 54,400,000

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66

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 33

VALOR NOMINAL: \$500

CAPITAL SUSCRITO: \$21,792,754,000

NUMERO DE ACCIONES: 43,585,508

VALOR NOMINAL: \$500

CAPITAL PAGADO: \$21,792,754,000

NUMERO DE ACCIONES: 43,585,508

VALOR NOMINAL: \$500

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 12 DE MARZO DE 2009

INSCRIPCION: 18 DE MARZO DE 2009 BAJO EL NRO. 3193 DEL LIBRO IX

CONSTA LA SITUACION DE CONTROL

SOCIEDAD CONTROLANTE

DENOMINACION: INVERSIONES TQ S.A.

NIT. 900.220.408-1

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE INVERSIONES TQ S.A. CORRESPONDEN A LA INVERSION EN SOCIEDADES MERCANTILES DE CUALQUIER NATURALEZA O ESPECIE, BIEN SEA NACIONALES O EXTRANJERAS QUE TENGAN COMO OBJETO SOCIAL LA FABRICACION, ENVASADO, DISTRIBUCION Y COMERCIALIZACION EN GENERAL DE PRODUCTOS BIOLOGICOS Y QUIMICOS; MEDICAMENTOS O PRODUCTOS FARMACEUTICOS, PERFUMERIA O EFECTOS DE TOCADOR; PRODUCTOS VETERINARIOS, AGRICOLAS; ALIMENTOS NATURALES O PROCESADOS; PRODUCTOS DE CONSUMO POPULAR Y SERVICIOS EN GENERAL.

SOCIEDAD CONTROLADA

DENOMINACION: TECNOQUIMICAS S.A.

NIT. 890.300.466-5

DOMICILIO: CALI

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LAS ACTIVIDADES DE TECNOQUIMICAS CORRESPONDEN 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 Y PRODUCTO DE CONSUMO POPULAR DE CUALQUIER NATURALEZA.

SUBORDINACION. INVERSIONES TQ S.A. TIENE SUSCRITAS Y PAGADAS ACCIONES EN TECNOQUIMICAS S.A. EN PORCENTAJE EQUIVALENTE AL 94.90% DEL CAPITAL SUSCRITO Y

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 34

PAGADO DE DICHA SOCIEDAD, LO QUE CONFIGURA SITUACION DE SUBORDINACION EN LA QUE LA PRIMERA ES LA MATRIZ Y LA SEGUNDA LA FILIAL.

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 14 DE SEPTIEMBRE 2009

INSCRIPCIÓN: 18 DE SEPTIEMBRE DE 2009 NRO.10818 DEL LIBRO IX

CONSTA EL GRUPO EMPRESARIAL:

MATRIZ: TECNOQUÍMICAS S.A.

NIT: 890300466-5

DOMICILIO: SANTIAGO DE CALI.

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: DEDICADA A LAS SIGUIENTES ACTIVIDADES: LA FABRICACIÓN, EL ENVASADO, LA IMPORTACIÓN, LA EXPORTACIÓN, LA VENTA Y DISTRIBUCIÓN DE PRODUCTOS BIOLÓGICOS Y QUÍMICOS, MEDICAMENTOS O PRODUCTOS FARMACÉUTICOS, PERFUMERÍA O EFECTOS DE TOCADOR, PRODUCTOS VETERINARIOS Y PRODUCTO DE CONSUMO POPULAR DE CUALQUIER NATURALEZA.

SUBORDINADA: ADHESIVOS INTERNACIONALES S.A.-ADHINTER S.A.

NIT: 805003416-4

DOMICILIO: CALI VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA LAS SIGUIENTES ACTIVIDADES: PRODUCCIÓN Y COMERCIALIZACIÓN 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 POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD ADHESIVOS INTERNACIONALES S.A.-ADHINTER S.A. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN, SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: INDUGRAFICAS S A S

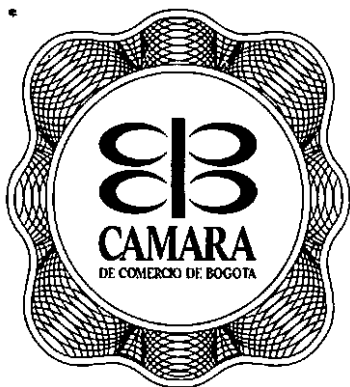
NIT: 890304375-1

DOMICILIO: CALI, VALLE DEL CAUCA.

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN AL DESARROLLO DE NEGOCIOS RELACIONADOS CON LAS ARTES GRÁFICAS, LA DISTRIBUCIÓN DE LAS MISMAS YA SEA DE SUS PRODUCTOS PROPIOS O POR CONTRATO, TANTO EN EL MERCADO NACIONAL COMO

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01

57

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 35

EN EL INTERNACIONAL.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD INDUGRAFICAS S A S Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: TECNOFAR TQ SAS

NIT: 817003055

DOMICILIO: VILLA RICA, CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA PRODUCCIÓN Y COMERCIALIZACIÓN DE MEDICAMENTOS, FARMACÉUTICOS, BIOLÓGICOS, COSMÉTICOS Y ARTÍCULOS DE TOCADOR, QUÍMICOS, VETERINARIOS, AGRÍCOLAS, PRODUCTOS DE ASEO PARA EL HOGAR Y ENVASES PLÁSTICOS PARA TODO TIPO DE USO.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD TECNOFAR TQ S A S Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: COLOMBIANA DE ADHESIVOS COLDESIVOS S.A.S

NIT: 890302608-3

DOMICILIO: CALI, VALLE DEL CAUCA

NACIONALIDAD: COLOMBIANA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES CORRESPONDIENTES A LA FABRICACIÓN, IMPORTACIÓN Y EXPORTACIÓN DE PRODUCTOS ADHESIVOS, ABRASIVOS Y AISLANTES Y DE CONSUMO POPULAR.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD COLOMBIANA DE ADHESIVOS COLDESIVOS S.A.S. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: TECNOQUÍMICAS DE ECUADOR S.A

DOMICILIO: DISTRITO METROPOLITANO DE QUITO, REPÚBLICA DE ECUADOR

NACIONALIDAD: ECUATORIANA

ACTIVIDAD: LA CUAL DESARROLLA LAS ACTIVIDADES DE VENTA AL POR MAYOR DE PRODUCTOS FARMACÉUTICOS, VETERINARIOS Y AGRÍCOLAS, DE SUSTANCIAS ADHESIVAS, COSMÉTICAS Y DE HIGIENE Y DE PRODUCTOS QUÍMICOS ORGÁNICOS E INORGÁNICOS.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 36

(50%) DEL CAPITAL DE LA SOCIEDAD TECNOQUIMICAS DE ECUADOR S.A. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26,27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: LABORATORIOS TERAMED S.A DE C.V.

DOMICILIO: SAN SALVADOR

NACIONALIDAD: SALVADOREÑA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA PRODUCCIÓN Y COMERCIALIZACIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD LABORATORIOS TERAMED S.A DE C.V. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: DISTRIBUIDORA PRINCIPAL S.A DE C.V.

DOMICILIO: SAN SALVADOR

NACIONALIDAD: SALVADOREÑA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA COMERCIALIZACIÓN Y DISTRIBUCIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO.

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD DISTRIBUIDORA PRINCIPAL S.A DE C.V Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: GALEMI S.A. DE C.V

DOMICILIO: SAN SALVADOR

NACIONALIDAD: SALVADOREÑA

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA COMERCIALIZACIÓN Y DISTRIBUCIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO.

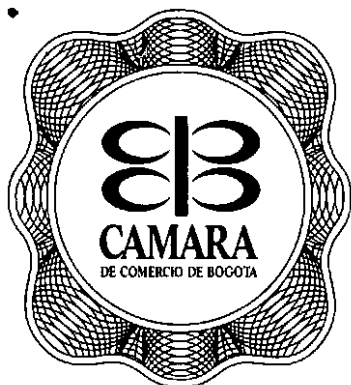
PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD GALEMI S.A DE C.V. Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y 28 DE LA LEY 222 DE 1995

SUBORDINADA: DROGUERÍA FARMACÉUTICA MONTREAL S.A.

DOMICILIO: GUATEMALA

NACIONALIDAD: GUATEMALTECA

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58

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 37

ACTIVIDAD: LA CUAL DESARROLLA ACTIVIDADES QUE CORRESPONDEN A LA COMERCIALIZACIÓN Y DISTRIBUCIÓN DE MEDICAMENTOS Y PRODUCTOS BIOLÓGICOS PARA CONSUMO HUMANO

PRESUPUESTO DE CONTROL: TECNOQUÍMICAS POSEE MAS DEL CINCUENTA POR CIENTO (50%) DEL CAPITAL DE LA SOCIEDAD DROGUERÍA FARMACÉUTICA MONTREAL S.A Y EXISTE ENTRE ELLAS UNIDAD DE PROPÓSITO Y DIRECCIÓN , SEGÚN LO PREVISTO EN LOS ARTÍCULOS 26, 27, Y 28 DE LA LEY 222 DE 1995

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: CL. 23 NRO. 7 39 DE CALI
RENOVO : POR EL AÑO 2011

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: CL. 23 NRO. 4 66 DE CALI
FECHA MATRICULA : 22 DE ABRIL DE 1992
RENOVO : POR EL AÑO 2011

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 2011

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 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO EL NRO.754339-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK FEMME
UBICADO EN: CL. 23 NRO. 7 34 DE CALI
FECHA MATRICULA : 19 DE DICIEMBRE DE 2008

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 38

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.754340-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK

UBICADO EN: CL. 23 NRO. 7 34 DE CALI

FECHA MATRICULA : 19 DE DICIEMBRE DE 2008

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.754341-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK VISION

UBICADO EN: CL. 23 NRO. 7 34 DE CALI

FECHA MATRICULA : 19 DE DICIEMBRE DE 2008

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.754342-2 ESTABLECIMIENTO DE COMERCIO: LABORATORIOS MK CARDIO

UBICADO EN: CL. 23 NRO. 7 34 DE CALI

FECHA MATRICULA : 19 DE DICIEMBRE DE 2008

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.761356-2 ESTABLECIMIENTO DE COMERCIO: ALMACEN VENTA A EMPLEADOS

UBICADO EN: CL. 23 NRO. 6 65 DE CALI

FECHA MATRICULA : 30 DE MARZO DE 2009

RENOVO : POR EL AÑO 2011

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 15 DE
MARZO DE 2011 .

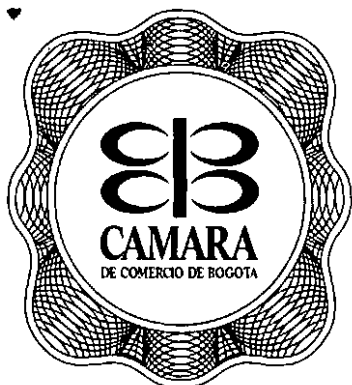
CERTIFICA:

QUE HACIENDA CALI FUE INFORMADO(A) EL 23 DE DICIEMBRE DE 2008 DE LA APERTURA
DEL ESTABLECIMIENTO DE COMERCIO. 754340-2 LABORATORIOS MK

QUE HACIENDA CALI FUE INFORMADO(A) EL 23 DE DICIEMBRE DE 2008 DE LA APERTURA
DEL ESTABLECIMIENTO DE COMERCIO. 754341-2 LABORATORIOS MK VISION

QUE HACIENDA CALI FUE INFORMADO(A) EL 23 DE DICIEMBRE DE 2008 DE LA APERTURA
DEL ESTABLECIMIENTO DE COMERCIO. 754339-2 LABORATORIOS MK FEMME

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01

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

FECHA: 2011/12/15

HORA: 13:47:46

OPERACION: 02C261215120

PAGINA: 39

QUE PLANEACION FUE INFORMADO (A) EL 06 DE ABRIL DE 2009 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 761356-2 ALMACEN VENTA A EMPLEADOS QUE LA SECRETARIA DE SALUD FUE INFORMADO (A) EL 06 DE ABRIL DE 2009 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 761356-2 ALMACEN VENTA A EMPLEADOS QUE HACIENDA CALI FUE INFORMADO(A) EL 06 DE ABRIL DE 2009 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 761356-2 ALMACEN VENTA A EMPLEADOS QUE HACIENDA CALI FUE INFORMADO(A) EL 23 DE DICIEMBRE DE 2008 DE LA APERTURA DEL ESTABLECIMIENTO DE COMERCIO. 754342-2 LABORATORIOS MK CARDIO

CERTIFICA:

QUE NO FIGURAN OTRAS INSCRIPCIONES QUE MODIFIQUEN TOTAL O PARCIALMENTE EL PRESENTE CERTIFICADO.

LOS ACTOS Y DOCUMENTOS REGISTRADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE SU INSCRIPCION, SIEMPRE Y CUANDO DENTRO DE DICHO TERMINO NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

DE CONFORMIDAD CON EL DECRETO 2150 DE 1.995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.

DADO EN CALI A LOS 15 DIAS DEL MES DE DICIEMBRE DEL AÑO 2011 HORA: 01:47:20 PM

[Firma manuscrita]

80

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -



RECIBO DE CAJA

No. 11 - 123076

Bogotá D.C., Diciembre 19 de 2011 - 15:57:32

RECIBIDO DE : REYES Y REYES ABOGADOS

NI 900.048.328

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	418721531	19/12/2011	780.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12	MARCAS Y LEMAS COMERCIALES
			304.000.00	304.000.00
				\$304.000.00

SON: **TRESCIENTOS CUATRO MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 10-082162- -00007-0000

Fecha: 2011-12-19 16:31:23 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 61

Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 0513240

Diciembre 19 de 2011 - 15:57:33

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 11 - 123079
		Bogotá D.C., Diciembre 19 de 2011 - 15:57:32

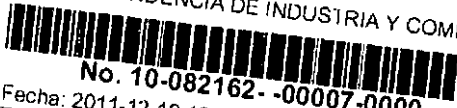
RECIBIDO DE : REYES Y REYES ABOGADOS NI 900.048.328

*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	418721531	19/12/2011	780.000.00

*** Conceptos Pagados ***			
CANT.	RENTISTICO	CONCEPTO	Vr. LINDITARIO Vr. CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	1608 N. CREACION PRORROGA DE TERMINOS O PLAZO ADICIONAL
			86.000.00 86.000.00
			===== \$86.000.00 =====

SON: **OCHENTA Y SEIS MIL PESOS MONEDA CORRIENTE**

Responsable: _____
Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-082162- -00007-0000
Fecha: 2011-12-19 16:31:23 Dep. 2020 DIR. NUEVASCR
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Act. 400 OPOSIOBSERVTER Folios: 61