



No. 14-167105- -00001-0000

Fecha: 2014-11-06 13:13:11 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 54

DIRECCIÓN DE NUEVAS CREACIONES
PRESENTACIÓN DE OPOSICIÓN

1. Oposición a solicitud de:

- ☒ Patente de invención
☐ Registro de Diseño Industrial
☐ Patente de Modelo de Utilidad
☐ Esquema de Trazado de Circuitos Integrados

Número de expediente: 14 167105

Solicitante: GLAXOSMITHKLINE LLC

Apoderado: CARLOS REINALDO OLARTE GARCIA

Título de la Nueva Creación: COMPRIMIDO ANTIÁCIDO

Gaceta: 702

2. Datos del Opositor

PROCAPS S.A.

☐

Persona Natural

☒ Persona Jurídica

Nombre o denominación /Razón social completa

WALTER TANAKA TATEKAWA

Nombre del representante legal

Documento de identificación: C.C. ☐ C.E. ☐ NIT ☒ Otro ☐ Cuál _____

Número 890106527-5 _____

Dirección: CALLE 80 78B 201 _____ Ciudad BARRANQUILLA

Teléfono 055 3719900 Fax: _____ Correo electrónico _____

- ☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del representante o apoderado:

MORENO BOHORQUEZ ELIANA ISaura

51.975.664

83823

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

Dirección del representante

CRA 13 119-95 OFICINA 104

Dirección electrónica
negocios@optimum-co.com

No. Fax
(571)6121979

Número telefónico
(571)2131213

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general:

4. Fundamentos de la oposición

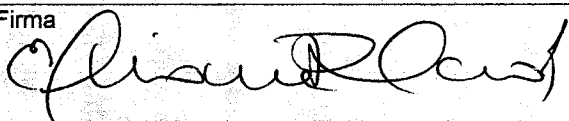
Causal: Art14, 16, 18,20 y 30 de la decisión 486 de la CAN no cumple con los requisitos De patentabilidad.

Justificación: La presente solicitud no cumple con los requisitos de patentabilidad dado que lo revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la misma tal y como se demostrará en el capítulo "fundamento de hecho".

Prórroga: SI ☐ NO ☐

5. Anexos

- ☒ Comprobante de pago de la tasa.
- ☒ Poder, si fuera el caso.
- ☒ Fundamentos de la oposición. Se anexan 6 folios (obligatorios indicar cuántos).
- ☒ Anexo de fundamentos de la oposición. Se anexan folios (obligatorios indicar cuántos)
- ☒ Copias para traslado.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

6. Firma	
Nombre del Firmante	Firma
ELIANA ISaura MORENO BOHORQUEZ	
CC. 51.975.664	Tarjeta Profesional: 83823

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800.176.089-2

- / -



RECIBO DE CAJA

No. 14 - 101341

Bogotá D.C., Septiembre 23 de 2014 - 12:59:05

RECIBIDO DE : PROCAPS S.A.

NI 890.106.527

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	633199755	23/09/2014	1.705.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1	50005-01-04 PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 OPOSICION POR CADA CLASE-MARCAS Y LEMAS COMERCIALES	335.000.00	335.000.00
				\$335.000.00

=====

SON: **TRESCIENTOS TREINTA Y CINCO MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 14-167105-00001-0000

Fecha: 2014-11-06 13:13:11 Dep. 2020 DIR.NUEVASCR
 Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
 Act. 400 OPOSIOBSERVTER Folios: 54

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) 6513240

Septiembre 23 de 2014 - 12:59:05

Señor Director,
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 14 167105
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPRIMIDO ANTIÁCIDO"
Solicitante : GLAXOSMITHKLINE LLC.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 702 del 11 de Agosto de 2014

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

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará

más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **carbonato de calcio**. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

- 2.1. La solicitud objeto de la presente fue presentada el 31 de julio de 2014, reivindicando prioridad bajo la solicitud US201261594055P del 2012-02-02; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 702 del 11 de Agosto de 2014, cuya publicación internacional corresponde a la WO2013116477 (A1) del 2013-08-08.
- 2.2. La solicitud colombiana 14 167105 objeto de la presente oposición se refiere a un comprimido oral antiácido que comprende al menos aproximadamente 60% en peso de carbonato de calcio granulado directamente compresible y un saporífero intenso. El comprimido puede tener una dureza de al menos aproximadamente 22 unidades Strong-Cobb y el comprimido puede tener una masa de entre aproximadamente 500 mg y aproximadamente 1.000 mg. Los comprimidos de la presente invención reducen o eliminan los síntomas de la acidez estomacal y también refrescan el aliento.
- 2.3. En primera instancia, se debe advertir que las reivindicaciones también se refieren a usos y métodos de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- “*Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)*”, los usos no están contemplados como patentables; y, Artículo 20.- “*No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*”. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente métodos de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US5880106 publicada el 9 de marzo de 1999.
- D2: US20020150617 publicada el 17 de Octubre de 2002.

2.5. Ahora bien, el documento D1, se refiere a formulaciones de dosificación oral para derivados nucleósidos didesoxi de purina lábiles en medio ácido, tales como ddA, ddI, y ddG, que han desarrollado mediante la incorporación de sistemas de tamponamiento insolubles en agua seleccionados en la formulación. Según D1, estas formulaciones proporcionan unidades de dosificación de masa en forma de cómoda, agradable al paladar masticable en comprimidos dispersables o una bolsita de polvo seco que comprenden un agente antiácido de magnesio insoluble o bien carbonato de sodio o calcio dihidroxialuminio carbonato. D1 enseña una tableta oral antiácido (pastilla oral antiácido, Col. 3, líneas 22-43; Col. 5, líneas 5-15; y, reivindicación 1) que comprende: carbonato de calcio (carbonato de calcio, reivindicación 1; Col. 9, línea 35-Col. 10, línea 46); y un aroma intenso (un aromatizante, tal como gaulteria, Col. 6, líneas 10-14; y, reivindicaciones 1 y 22); en el que el comprimido tiene una dureza de al menos aproximadamente 22 Unidades Strong Cobb (tabletas se compactaron a una dureza de 16 a 24 Strong-Cobb, Col. 9, líneas 9-13).

2.6. Por otro lado, la anterioridad D2 proporciona un método de hacer composiciones de comprimidos que están sustancialmente libres de excipientes. Este documento revela al menos aproximadamente 60% en peso de carbonato de calcio granulado directamente comprimible (0,5 a 97 por ciento en peso de uno o más compuestos terapéuticos adicionales, es decir, el tercer compuesto terapéutico, que puede ser



carbonato de calcio OC, es decir, carbonato de calcio directamente comprimible:
Párrafos: [0025] - [0026]; [0072]; [0107] - [0108], Tabla 7; y, reivindicaciones 1 y 12).

2.7. Por tanto, es evidente para un experto normal en la técnica en el momento de la invención, modificar el documento D1 para usar la cantidad deseada de carbonato de calcio con un relleno mínimo, tal como carbonato cálcico directamente compresible, según lo enseñado por D2. La motivación para hacerlo sería lograr la capacidad óptima antiácida de la tableta (D1: Col. 3, líneas 45-56; Col. 4, líneas 36-54; Col. 5, líneas 48-60) con un mínimo de excipientes para reducir el peso y el volumen de las tabletas (D2: Párrafos. [0069] - [0071]). D1, no revela explícitamente en el que el comprimido tiene una masa de entre aproximadamente 500 mg y aproximadamente 1000 mg. Sin embargo, D2 enseña que el comprimido tiene una masa de entre aproximadamente 500 mg y aproximadamente 1000 mg (la composición se compacta en una tableta con una masa de 100 mg a 2000 mg, Párrafos: [0028]; y, [0069]). Por tanto es evidente para un experto normal en la técnica en el momento de la invención modificar D1 para limitar la cantidad de excipientes con el fin de compactar la tableta a la masa deseada, según lo enseñado en D2. La motivación para hacerlo sería la de formar una tableta de peso óptimo y el volumen que tiene las propiedades deseadas, tales como resistencia, dureza, desintegración y liberación de compuestos terapéuticos tras la administración (D1: Párrafos [0028], [0065]; y, [0070] - [0071]). De igual forma, D1 enseña que hay al menos aproximadamente 70% en peso de carbonato de calcio granulado directamente comprimible (0,5 a 97 por ciento en peso de uno o más compuestos terapéuticos adicionales, es decir, la tercera compuesto terapéutico, que puede ser OC carbonato de calcio, es decir, directamente compresible, párrafos: [0025] - [0026]; [0072]; [0107] - [0108], Tabla 7; reivindicaciones 1 y 12).

2.8. Como se evidencia, en vista de lo revelado en D1 con las modificaciones presentadas en D2 un experto en la materia, podría obviamente llegar a conformar la forma oral según la presente solicitud, por lo que carece evidentemente de altura inventiva.

2.9. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 14 167105 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.



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

2.8.1 CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 2 de febrero de 2012, un experto en la materia habría podido deducir de manera obvia, el hecho de modificar D1 para limitar la cantidad de excipientes con el fin de compactar la tableta a la masa deseada, según lo enseñado en D2 para llegar a una tableta de peso óptimo y el volumen que tiene las propiedades deseadas, tales como resistencia, dureza, desintegración y liberación de compuestos terapéuticos tras la administración, sobre lo cual busca protección en el presente capítulo reivindicatorio.

2.8.2 CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman un método de tratamiento y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a métodos de tratamiento, no cumple con el requisito de la aplicación industrial.

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



aplicación industrial.”. La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10 Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada “**COMPRIMIDO ANTIÁCIDO**”, cuyo titular **GLAXOSMITHKLINE LLC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 702 del 11 de Agosto de 2014.

3. PRUEBAS

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

- D1: US5880106 publicada el 9 de marzo de 1999.
- D2: US20020150617 publicada el 17 de Octubre de 2002.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Artículo 45 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.2. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US5880106 publicada el 9 de marzo de 1999.
 - D2: US20020150617 publicada el 17 de Octubre de 2002.

6. NOTIFICACIONES

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

Señor Superintendente,



ELIANA ISaura MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

ANEXO 1



US005880106A

United States Patent [19]

Ullah et al.

[11] **Patent Number:** **5,880,106**[45] **Date of Patent:** **Mar. 9, 1999**[54] **ORAL DOSING FORMULATIONS OF
DIDEOXY PURINE NUCLEOSIDES**[75] Inventors: **Ismat Ullah**, Cranbury; **Shreeram
Narahari Agharkar**, Princeton; **Gary
James Willey**, Jackson, all of N.J.[73] Assignee: **Bristol-Myers Squibb Company**,
Princeton, N.J.[21] Appl. No.: **942,660**[22] Filed: **Oct. 2, 1997****Related U.S. Application Data**[63] Continuation-in-part of Ser. No. 882,204, May 13, 1992,
abandoned, which is a continuation-in-part of Ser. No.
733,547, Jul. 22, 1991, abandoned.[51] **Int. Cl.⁶** **A61K 31/70**[52] **U.S. Cl.** **514/45; 514/46; 536/27.14**[58] **Field of Search** **514/45, 46; 536/27.14**[56] **References Cited****U.S. PATENT DOCUMENTS**

4,260,596	4/1981	Mackles	424/14
4,786,505	11/1988	Lovgren et al.	424/81
4,861,759	8/1989	Mitsuya et al.	514/46
4,935,243	6/1990	Borkan et al.	424/441
5,026,687	6/1991	Yarchoan et al.	514/45
5,087,447	2/1992	Racz et al.	424/81

FOREIGN PATENT DOCUMENTS

0 138 540	4/1985	European Pat. Off.
0138540	4/1985	European Pat. Off.
2 082 456	3/1982	United Kingdom
2082456	3/1982	United Kingdom
8802629	4/1988	WIPO
9109605	7/1991	WIPO

OTHER PUBLICATIONSAnderson, et al., *International J. of Pharmaceutics*, 1988, 45:
27-37.Hoofnagle, et al., NTIS Publication PB89-186217, Method
of Treatment of Hepatitis May 1989.McGowan, et al., *Reviews of Infect. Diseases*, 1990, Over-
view of the Preclinical Devel. of an Antiretroviral Drug, 2',3'
-Dideoxyinosine. 12 (Supplement 5) : S 513-S 521. (Jul.).
Dolin, et al., *Reviews of Infect. Diseases*, (1990) 12 Supp
5:S540-S549, 2',3'-Dideoxyinosine in Patients with AIDS
or AIDS-Related Complex. (Jul.).Hartman, et al., *Clin. Pharmacol. Ther.* (1991) 50: 278-285,
II. The Effects of Different Oral Formulations and the
Presence of Other Medications.Anderson et al., "Preformulation Solubility and Kinetic
Studies of 2',3'-Dideoxypurine Nucleosides: Potential Anti-
-AIDS Agents," *International Journal of Pharmaceutics*,
45, 27-37 (1988).Hoofnagle et al., "Method of Treatment of Hepatitis," *NTIS
Publication PB89-186217*, Specification of US Patent
Application 07/351,502; Patent Application Filing Date—
May 15, 1989.McGowan et al., "Overview of the Preclinical Development
of an Antiretroviral Drug, 2', 3'-Dideoxyinosine," *Reviews
of Infectious Diseases*, 12(Suppl. 5), S513-S521 (Jul.-Aug.
1990).Dolin et al., "2', 3'-Dideoxyinosine in Patients with AIDS or
AIDS-Related Complex," *Reviews of Infectious Diseases*,
12(Suppl. 5), S540-S549 (Jul.-Aug. 1990).Hartmann et al., "Pharmacokinetics of 2', 3'-Dideoxyinosine
in Patients with Severe Human Immunodeficiency Infection.
II. The Effects of Different Oral, Formulations and the
Presence of Other Medications," *Clin. Pharmacol. Ther.*,
50(3), 278-285 (Sep. 1991).Yarchoan et al.(II), "In Vivo Activity Against HIV and
Favorable Toxicity Profile of 2', 3'-Dideoxyinosine," *Sci-
ence*, 245, 412-415 (Jul. 28, 1989).Rudnic et al., "Oral Dosage Forms," Ch. 89 in *Remington's
Pharmaceutical Sciences, 18th Edition*, Gennaro et al.(eds.),
Philadelphia College of Pharmacy and Science, Philadel-
phia, PA, 1990, only pp. 1633-1638 supplied.**Primary Examiner**—Marian C. Knode**Assistant Examiner**—L. Eric Crane**Attorney, Agent, or Firm**—Richard P. Ryan[57] **ABSTRACT**Improved oral dosage formulations for acid-labile dideoxy
purine nucleoside derivatives such as ddA, ddI, and ddG,
have been developed by incorporating selected water-

ORAL DOSING FORMULATIONS OF
DIDEOXY PURINE NUCLEOSIDES

CROSS REFERENCE TO RELATED
APPLICATION

This is a continuation-in-part application of U.S. Ser. No. 07/882,204 filed May 13, 1992 now abandoned, which is a continuation-in-part application of U.S. Ser. No. 07/733,547 filed on Jul. 22, 1991 and now abandoned.

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical compositions which provide convenient, palatable oral dosage formulations for the acid-labile dideoxy purine nucleosides such as 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, and 2',3'-dideoxyguanosine. More specifically, it relates to inclusion of specific antacid buffers which confer special advantages such as increased bioavailability, lower variability in bioavailability between patients, greater convenience, lessened potential for gastrointestinal distress, and higher patient acceptability.

Compositions containing 2',3'-dideoxyadenosine (ddA), 2',3'-dideoxyinosine (ddI), and 2',3'-dideoxyguanosine (ddG), and their triphosphates for treating retroviral infections have been disclosed. Mitsuya, et al., in U.S. Pat. No. 4,861,759 disclose the oral administration of these dideoxy purine nucleosides in the form of liquids or tablets containing antacid buffering agents so that the pH of the resultant composition is in the neutral (pH 6-pH 8) range. Specifically exemplified and claimed is an oral gavage formulation containing 0.1N acetate buffer with a pH of 6.8 to 7.2. Enteric coating of the tablets is also disclosed as an option.

The acid lability of the 2',3'-dideoxypurine nucleosides is well-known in the art and for that reason their oral administration typically requires administration on an empty stomach after ingestion of antacids. Prevention of acid-catalyzed hydrolysis of parent drug is important for these agents because their potent antiviral activity is lost in their hydrolysis by-products. Approaches to improving the acid stability of these acid-labile nucleoside derivatives have involved enteric-coated formulations, inclusion of a buffer in the pharmaceutical dosage form, and neutralization of the gastrointestinal tract just before drug ingestion by pretreatment with commercial antacids such as Maalox® or Mylanta®. Studies reported by McGowan, et al. in *Reviews of Infectious Diseases*, Vol. 12, Supp. 5, 5513-521 (1990) indicated that for ddI a superior approach for oral administration involves formulation of the drug at selected dose levels in combination with a fixed amount of citrate-phosphate buffer as a powder mixture. This dry mixture is enclosed in foil to provide a sachet (the "CP sachet") that must be mixed and diluted with liquid before oral ingestion.

Formulation approaches involving enteric coatings were not promising. Enteric coatings tended to reduce the nucleoside drug's bioavailability and depress peak plasma levels. High peak plasma levels of active drug are an important requirement for its clinical antiviral activity. Enteric coated formulations also were especially susceptible to a meal effect, further reducing bioavailability.

The citrate-phosphate buffered ddI formulations, which allow oral dosing, were preferred clinically for long-term therapy over the earlier available lyophilized dosage form of the drug which requires reconstitution prior to intravenous administration. These oral powder formulations for reconstitution consist of varying ddI levels combined with the same amount of buffering ingredients (about 10 g per day)

regardless of final drug dose strength. All dose strength formulations thus have the same acid neutralization capacity. However, the powder blend sachets are bulky (about 20 g/dose) and inconvenient - their use causes some patient inconvenience. Reconstitution is always required prior to administration and results in a large volume of constituted solution (due to 20 g of solute) to be ingested. This salty solution can cause diarrhea and the required ingestion of about 10 g per day of soluble antacid buffers may result in systemic alkalosis when administered on a long-term basis as required, for example, in treating HIV infections.

A comparison of available oral formulations of ddI was recently reported (Hartman, et al., "Pharmacokinetics of 2',3'-dideoxyinosine in patients with severe human immunodeficiency infection. II. The effects of different oral formulations and the presence of other medications," *Clin. Pharmacol. Ther.*, 1991; 50:278-85). With the maximum bioavailability of any buffered preparation being reported as $\leq 40\%$, the reference concludes that "an optimal preparation remains to be found." Of existing formulations, the "CP sachet" appeared to be the best oral preparation although its use caused reported diarrhea and/or hypokalemia in some patients.

It was an object of the present invention to provide pharmaceutical compositions for these acid-labile nucleoside derivatives which would allow convenient oral administration of reduced mass dosage formulations such as tablets which could be chewed and swallowed or readily dispersed in liquid for ingestion. Such a composition would also allow formulation of reduced mass sachet dosage forms.

Another objective was to find a combination of antacid buffers effective in preventing acid hydrolysis of the nucleosidic agent but whose effect on diarrhea and/or electrolyte and pH imbalances would be minimized.

A further object of the invention was to provide a pleasant tasting composition with high levels of patient acceptance and tolerability. A key to realization of these objects was in providing in a reduced mass form the same amount of bioavailable drug delivered by the bulky dry powder blend provided in the citrate-phosphate buffer sachets. Surprisingly, improved buffer systems comprising certain water-insoluble aluminum or calcium carbonates in combination with water-insoluble magnesium antacids were found to increase drug bioavailability by about 20 to 25%. Addition of reduced amounts of compatible sweetening and flavoring agents for incorporation into the improved drug-buffer composition also contributed to achieving the objects of the invention.

SUMMARY DESCRIPTION OF THE
INVENTION

Improved pharmaceutical compositions have been discovered which allow the oral administration of the acid-labile dideoxy purine nucleoside derivatives in the form of reduced mass powder sachets and preferably as convenient palatable oral tablets. These tablets are also readily dispersible in liquids to offer an optional route of ingestion. The crux of the present invention lies in the unobvious selection of certain water-insoluble antacids to provide the unique buffering action, allowing reduced mass of the formulation while providing increased bioavailability, enhanced palatability and decreased gastrointestinal side-effects. Successful tablet formulation resulted from selection and development of compatible water-insoluble antacid buffer systems, which when combined with sweetening agents, flavoring

agents, and other optional excipients deliver drug at a higher bioavailability than realizable in previous oral formulations, thereby permitting presentation in the more convenient and acceptable reduced mass form of a sachet or a chewable/dispersible tablet.

BRIEF DESCRIPTION OF THE DRAWING

FIG. 1 discloses a semi-logarithmic plot of the degradation of Didanosine (ddI) as a function of pH and time at 37° C.

DETAILED DESCRIPTION OF THE INVENTION

The present invention concerns an improvement in oral dosage formulations of acid-labile dideoxy purine nucleoside derivatives, e.g. ddA, ddI, and ddG. This formulation improvement concerns incorporation of the active drug ingredient in a reduced mass acid buffer formulation which can be provided as convenient palatable tablets that can be chewed and swallowed or easily dispersed in appropriate non-acidic liquids and then ingested. Reduced mass powder formulations in sachet form are also intended.

In order to formulate these acid-labile drugs as reasonably-sized convenient chewable/dispersible tablets, a pharmaceutical composition was required that would provide sufficient bioavailable drug in a palatable but non-bulky form. It was discovered that use of certain insoluble antacid buffers in combination gave a buffer system which actually provided an increase of drug bioavailability with reduced variability between human subjects, compared with previous oral formulations. The improved antacid buffering performance of the insoluble antacid agents/combinations of the present invention is surprising in that it does not depend simply on "buffering capacity" which can be calculated stoichiometrically. Compared to previously used dideoxynucleoside-buffer systems, smaller amounts of the new systems provided increased bioavailability of the dideoxynucleoside such as ddI. In addition, the new combination antacid buffer systems have improved palatability thereby making possible the use of reduced amounts of sweetening and flavoring agents, further contributing to the reduction in formulation weight. Use of the new antacid buffers also result in a lowered potential for diarrhea or constipation which commonly result from chronic administration of many antacid agents.

The term "water-insoluble buffers," as applied to antacid agents which may be used in the instant buffer system, include antacids which have low water solubility as well as those which are generally insoluble. The combination buffer systems of this invention are, in general, comprised of mixtures of water-insoluble antacid magnesium compounds with dihydroxyaluminum alkali metal carbonates or calcium carbonate. Preferred mixtures comprise about one part of a water-insoluble antacid magnesium compound in combination with about 2 to 4 parts of a dihydroxyaluminum alkali metal carbonate or with about 1.5 to 3 parts of calcium carbonate which is most preferred.

The water-insoluble antacid magnesium compound can be selected from magnesium carbonate, magnesium carbonate hydroxide, magnesium hydroxide, magnesium oxide, magnesium phosphate (tribasic), and magnesium trisilicate; or a combination of these to comprise the magnesium antacid component. Magnesium oxide and magnesium hydroxide are preferred, with magnesium hydroxide being the most preferred compound. The dihydroxyaluminum alkali metal carbonates refer chiefly to dihydroxyaluminum potassium carbonate and dihydroxyaluminum sodium carbonate, which is preferred.

The present invention was developed in part by employing an in vitro model of a gastric system to measure acid neutralization. While the acid neutralization capacity can be readily calculated and measured using standard titration procedures, it is the rate of neutralization and maintenance-stability of the pH value that is of paramount importance with respect to nucleosidic drug stability.

The range of ratios of the insoluble aluminum and calcium antacid buffer agents, such as dihydroxyaluminum alkali metal carbonate and calcium carbonate, to the insoluble magnesium antacid buffer agent also reflects a balance between the diarrhea-promoting characteristics of the magnesium component and the constipation-causing characteristics of the aluminum and calcium components. Additionally, the instant combinations provide superior acid neutralizing properties which are very important given the limited quantities of buffer that can be used due to weight restrictions for tablet formulations.

Another feature of the improved combination antacid buffer systems concerns the resultant gastric acidity following administration. For the dideoxy purine nucleosides, a pH of about 5 would appear to be the lower limit below which the drugs undergo rapid acid-catalyzed hydrolysis. A desirable buffer system would therefore maintain the stomach pH above 5 for at least half an hour but preferably for about an hour. It is also desirable, as achieved with these new buffer systems, that the stomach pH not rise much above 5 in order to limit the potential for physiologic pH imbalance (alkalosis) in the gastrointestinal tract. The combination antacid buffer systems of the present invention were selected initially using an acid neutralization rate test which will be described in greater detail infra. It is well known that strongly basic compounds can give rise to GI alkalosis with repeated ingestion.

The unique synergistic characteristics of the selected insoluble aluminum and/or calcium carbonate compounds of the new combination buffer systems are demonstrated by the results obtained when aluminum hydroxide, a widely-used antacid, was substituted for the selected aluminum/calcium component of the new buffer combinations. The aluminum hydroxide-containing buffer system was inferior to the instant buffer systems as it gave increased acidic pH values when studied in an in vitro gastric secretion test, even when additional aluminum hydroxide suspension was added. In contrast, the use of dihydroxyaluminum sodium carbonate or calcium carbonate combined with an insoluble magnesium compound gave time extended pH values in the desired range (above pH 5 but not strongly basic) when studied in the in vitro gastric secretion system, indicative of its more efficient acid neutralization. This also demonstrates that simple neutralization equivalency will not distinguish between antacid agents insofar as the desired performance is concerned.

In some of the instant formulations a water-soluble antacid buffer, such as a phosphate or citrate salt such as sodium citrate, may also be added. These soluble antacid buffers would be provided in a lesser amount, generally representing less than about a quarter of the total amount of buffer. In general, only the water-insoluble buffer systems are preferred.

Finally, the importance of the new improved combination buffer systems can be appreciated in terms of improved palatability. Selection of the insoluble antacid buffers comprising these novel pharmaceutical compositions provide superior acid neutralization capacity while having organoleptic properties which minimize the amounts of sweetening

and flavoring agents required for palatability. In this way formulation weight is kept low as only small amounts of sweetening and flavoring ingredients are necessary to meet taste acceptance.

In similar fashion, as for the previous citrate-phosphate buffer dry powder sachet formulations, the water-insoluble antacid buffers are provided at a constant level, independent of the drug dose to be incorporated in the instant pharmaceutical compositions. The improved buffer systems of the new formulations reduce the total amount of antacid ingested daily (about 10 g) in prior clinical formulations to a range of about 3 to 8 g daily in the reduced mass formulations, either sachets or chewable dispersible tablets at recommended dose levels. This reduction in daily antacid intake is beneficial to the GI system.

Due to the increased bioavailability of drug substance achieved in these new pharmaceutical compositions, less drug may be used to give potencies equivalent to the previous "CP sachet" sachet dosage forms. Clinical studies conducted with ddI demonstrated the bioavailability advantage for the new formulations. As can be seen, two tablets formulated from the improved pharmaceutical compositions can be given in place of a sachet dose as shown in Table 1. The increased bioavailability of the drug substance also contributes to lower tablet weight.

Table 1

Dose Equivalencies of ddI Chewable/Dispersible Tablets to Citrate/Phosphate Buffer Sachets

- Two 150 mg ddI tablets (300 mg) equivalent to a 375 mg sachet.
- Two 100 mg ddI tablets (200 mg) equivalent to a 250 mg sachet.
- Two 50 mg ddI tablets (100 mg) equivalent to a 167 mg sachet.
- Three 25 mg ddI tablets (75 mg) equivalent to a 100 mg sachet.

As shown in Table 1, the dose weight of ddI may be reduced by about 20-25% when given in the new chewable/dispersible tablet formulations compared to the old "CP" sachet form.

The improved oral pharmaceutical compositions of this invention contain then from about 5 to 375 mg of a 2',3'-dideoxy purine nucleoside derivative such as ddA, ddI, and ddG per tablet and from about 10 to 375 mg per sachet unit. There is also provided in these compositions, sufficient antacid buffer, generally in the range of about 800 to 2800 mg, comprised of a water-insoluble antacid magnesium compound in combination with a dihydroxyaluminum alkali metal carbonate or calcium carbonate; so that adequate antacid capacity is achieved by the ingestion of two tablets or one reduced mass sachet as a per dose. Desired sweetener agent, flavor and tableting excipients may be incorporated. More detailed specification of the mixed water-insoluble antacid buffer systems as well as other ingredients that may be incorporated into these novel dideoxy nucleosidic pharmaceutical compositions is given in the specific embodiments described infra.

Another aspect of the present invention concerns the palatability of the oral tablet formulation. The taste characteristics of the water-insoluble antacid buffers selected for use in the present invention are such that their incorporation into the present pharmaceutical compositions facilitates the objective of tablet palatability by reducing the demand for ingredients to mask the taste of the buffer system itself. A

sweetener component was selected which is comprised of aspartame to which sucrose or sorbital may be optionally added to enhance the palatability according to the specific antacid compounds selected for the final composition. In general, little if any sucrose is added when calcium carbonate is selected as an antacid buffer component. From about 2 to 5 parts of sucrose per part of aspartame is preferred when dihydroxyaluminum sodium carbonate is an ingredient.

Selection of flavoring agents also may be varied depending upon the specific antacid compounds being used. Taste tests were employed to obtain the best tasting flavored compositions. Wintergreen, orange and mandarin orange flavorings are preferred.

Other pharmaceutical additives may also be incorporated. Although traditional chewable tablets do not require a disintegrant, one may be incorporated into these compositions in order to insure rapid disintegration when dosing as a dispersion is intended, as well as a rapid rate of acid neutralization after oral administration. Commercial disintegrants such as Polyplasdone XL and Explotab may be used. Glidants, such as silicon dioxide, and lubricants, such as magnesium stearate, may also be incorporated optionally into the pharmaceutical compositions of the present invention. The use of these and other pharmaceutical excipients is well known in the art. Similarly the formulation process and tableting operations would be considered standard practice in the pharmaceutical art.

For clinical use, two chewable/dispersible tablets, having the selected strengths of drug per tablet deemed appropriate by the attending or prescribing medical practitioner, will be chewed thoroughly either together or in rapid succession. A rinse of about 4 oz. (120 ml) of non-acidic liquid such as water may also be given. Alternatively, the two tablets may be thoroughly dispersed in at least one ounce of water and the dispersion then taken orally. To improve palatability and/or provide a taste change, the aqueous dispersion can be doubled or tripled in volume by the addition of another liquid such as milk, flavored milk, or a fruit juice. These mixed dispersions may be stored for up to an hour at room temperature prior to ingestion.

The tablets or dispersion may be given once or twice daily and preferably be ingested on an empty stomach twice daily. This means at least 30 minutes before eating or 2 hours after eating. This dosing regimen is offered as a guide to clinical use with the realization that the practice of medicine is individualized and medical practitioners may depart from this general guide according to their treatment practice with individual patients. Similarly the level of drug to be administered will be that which the medical practitioner feels is appropriate for the patient being treated, taking into account severity of disease, age and condition of patient and other relevant medical parameters.

In summary, the improved pharmaceutical compositions developed for oral administration of the acid-labile dideoxy purine nucleosides give reduced weight dosage formulations with unexpectedly improved drug bioavailability, lower variability between patients, and with better palatability relative to prior formulations. These characteristics allow the formulation of reduced mass sachets and chewable/dispersible tablet formulations with their increased convenience and patient preference. The greater patient convenience associated with the use of oral tablets is felt to have a beneficial effect on patient compliance with their drug regimen. To patients that might have problems in chewing or swallowing, the dispersibility of the tablets is a further advantage.

5,880,106

7

The following examples describe in detail test methods and procedures for preparation of pharmaceutical compositions and formulations of the present invention. It will be apparent to those skilled in the art that many modifications, both of methods and materials and amounts, may be practiced without departing from the purpose and intent of this disclosure. From the foregoing description and the following examples it is believed that one skilled in the art is able to use the invention to the fullest extent.

EXAMPLE 1

Acid Neutralization Rate—Test Method

This test was developed to determine rate and duration of acid neutralization and to measure efficiency of the formulations to maintain the desired pH. This test was performed using a USP apparatus 11 dissolution assembly (paddle method). Into the dissolution vessel, 750 mL of purified water, USP was added and equilibrated to $37^{\circ}\pm 1^{\circ}$ C. Into this water, a calibrated pH probe was immersed, and 4.0 mL of 1.0N HCl was added, and the paddle stirrer, set at 100 RPM, was started. The contents were allowed to stir for at least two minutes before addition of the test sample. Test samples were prepared by dissolving/dispersing the test sample in a sufficient volume of water. A Harvard Infusion/Withdrawal Pump (model 940) was set up with a 30 mL syringe filled with 0.8214N HCl. The piston speed was adjusted to deliver 28 mL of solution per hour (23 mEq/hour). The test sample was added to the dissolution flask and the Harvard pump was started immediately. The solution container was rinsed with purified water, USP, and the volume was made to 972 mL. The media pH was recorded at selected time intervals over a period of one hour.

Compositions and Formulations

The following examples of pharmaceutical compositions and formulations employ ddl (generically known as Didanosine) as the representative drug member of the acid-labile nucleosides. This is because ddl has been approved for use in treating AIDS patients. The other acid-labile nucleosidic drug agents, e.g. ddA and ddG, could be readily substituted for ddl in the compositions and formulations.

The pharmaceutical compositions comprise, as a powder blend, didanosine and a buffer system which is itself comprised of an insoluble magnesium antacid compound, e.g. magnesium hydroxide, combined with either calcium carbonate or an insoluble aluminum antacid compound, e.g. dihydroxyaluminum sodium carbonate. Sweeteners, flavors, and other desirable excipients used in powder blends, as well as a water-soluble antacid, e.g. sodium citrate, may also be components. These pharmaceutical compositions are then formulated into oral dosing forms such as an oral powder suspension or chewable/dispersible tablets.

EXAMPLE 2

Oral Suspension Dosage Form (reduced mass sachet)

A preferred embodiment of a didanosine powder composition for an oral suspension dosage form is prepared as follows.

8

The following ingredients were weighed:

Ingredient	Weight
didanosine	7.6 Kg
magnesium hydroxide	14.0 Kg
dihydroxyaluminum sodium carbonate	42.0 Kg
sodium citrate dihydrate	12.0 Kg
sucrose powder	43.0 Kg
orange flavor	1.2 Kg

All ingredients are added in a tumbling type V-blender and then blended for 15 minutes. The blend is then milled through Fitzmill with hammers forward using #00 plate at medium chamber speed and medium feed rate. The milled material is blended again in tumbling type V-blender for 20 minutes. This bulk blend is then assayed for drug potency and content uniformity (found 378 mg didanosine/6.0 g powder weight and RSD of 0.9% for 10 samples with a range of 369.8 mg to 381 mg/6.0 g weight) and filled into unit dose foil packets using a Bartelt powder filling and sealing machine (model IMG-9). These foil packets will contain 6.0 g of didanosine oral suspension powder which can have the following compositions (depending on desired drug strength).

Ingredient	Weight
didanosine	0.005 g to 0.375 g
magnesium hydroxide	0.700 g
dihydroxyaluminum sodium carbonate	2.100 g
sodium citrate dihydrate	0.600 g
sucrose powder	Q.S.
orange flavor	0.060 g
Net Weight	6.000 g*

*Prior Art sachets contain 20 g of powder blend.

*Prior Art sachets contain 20 g of powder blend.

EXAMPLE 3

Chewable/Dispersible Oral Tablet

An embodiment of a didanosine chewable/ dispersible tablet formulation is prepared as follows.

The following ingredients were weighed:

Ingredient	Weight
didanosine	2.083 Kg
magnesium hydroxide	7.500 Kg
dihydroxyaluminum sodium carbonate	22.500 Kg
sodium citrate dihydrate	5.000 Kg
aspartame	0.667 Kg
polyplasdone XL10	1.250 Kg
powdered sucrose	2.667 Kg
microcrystalline cellulose pH 101	6.500 Kg
silicon dioxide	0.625 Kg
natural wintergreen flavor	0.375 Kg
magnesium stearate (for compaction)	0.625 Kg

All ingredients are placed in a tumbling type V-blender and blended for 10 minutes. The blend is then milled through Fitzmill with knives forward, using 1 B plate at medium chamber speed, and medium feed rate. The milled material is blended again in tumbling type V-blender for 10 minutes. The blend is slugged on twelve station Colton D3 tablet press. The slugs are milled through Fitzmill with knives forward, using #4 plate at slow chamber speed, and medium

9

feed rate. The milled slugs are then passed through oscillators using 16 mesh wire screen. The resulting granules are placed in a tumbling type V-blender to which calculated amount of magnesium stearate 0.0125 g/2.9875 g of granulation weight, and blended for 7 minutes. This blend is then assayed for drug potency and content uniformity (found 126 mg didanosine/ 3.0 g granulation weight and RSD of 1.0% for 10 samples with a range of 124 mg to 128 mg/3.0 g granulation weight. The granulation is compacted into tablets on twelve station D3 rotary tablet press using 7/8" round, flat beveled edge punches. Tablets are compacted to hardness of 16-24 Strong Cobb Units to a target weight of 3.0 g/tablet.

These tablet formulations then have the following compositions (depending on desired drug strength).

Ingredient	Weight
didanosine	0.005 g to 0.375 g
magnesium hydroxide	0.4500 g
dihydroxyaluminum sodium carbonate	1.3500 g
sodium citrate dihydrate	0.3000 g
aspartame	0.0400 g*
polyplasdone XL10	0.0750 g
powdered sucrose	0.1600 g
microcrystalline cellulose pH 101	Q.S.
silicon dioxide	0.0375 g
natural wintergreen flavor	0.0225 g
magnesium stearate (for compaction)	0.0375 g
magnesium stearate (for tableting)	0.0125 g
Net Weight	3.00 g

*0.0600 g aspartame to be used for 150 mg and higher strength didanosine tablets.

EXAMPLE 4

Aluminum, Sodium and Sugar Free Chewable/Dispersible Oral Tablet

A preferred embodiment of an aluminum, sodium and sugar free didanosine chewable/dispersible tablet formulation is prepared as follows.

Ingredient	Weight
didanosine	0.300 Kg
calcium carbonate	1.100 Kg
magnesium hydroxide	0.500 Kg
aspartame	0.120 Kg
polyplasdone XL10	0.150 Kg
silicon dioxide	0.040 Kg
microcrystalline cellulose	1.460 Kg
natural orange flavor	0.100 Kg
magnesium stearate (for slugging)	0.020 Kg
magnesium stearate (for tableting)	0.010 Kg

All ingredients are placed in a tumbling V-blender and blended for 10 minutes. The blend is then milled through Fitzmill with knives forward using #1 plate at medium chamber speed, and medium feed rate. The milled material is blended again in tumbling type V-blender for 10 minutes. The blend is slugged on single punch F-press. The slugs are milled through Fitzmill with knives forward, using #4 plate at slow chamber speed, and medium feed rate. The milled slugs are then passed through oscillator using 16 mesh wire screen. The resulting granules are placed in a tumbling type V-blender to which calculated amount of magnesium stearate 0.01 g/1.89 g of granulation weight and blended for 10 minutes. The blend is then compacted into tablets on single

10

punch F-press using 3/4" round, flat beveled edge punches. Tablets are compacted to hardness of 18-21 strong cell units to a target weight of 1.9 g/tablet.

As an example, tablet formulations have the following composition.

Ingredient	Amount (g) Per Tablet
didanosine	0.005 to 0.375
calcium carbonate (light)	0.550
magnesium hydroxide	0.250
aspartame	0.020 to 0.060*
polyplasdone XL10	0.075
silicon dioxide	0.020
microcrystalline cellulose	q.s.
natural orange flavor	0.050
magnesium stearate (for slugging)	0.010
magnesium stearate (for tableting)	0.005
Total Tablet Weight	1.900

*Amount of aspartame can vary with didanosine content and intermediate strength compositions contain proportional amounts of aspartame.

EXAMPLE 5

Chewable/Dispersible Oral Tablet #2

A more preferred embodiment of a didanosine chewable/dispersible tablet formulation can be prepared by appropriate modification of the procedure set forth in Example 4 to provide tablets having the following composition.

Ingredient	Amount (g) Per Tablet
didanosine	0.005 to 0.375
calcium carbonate (light)	0.550
magnesium hydroxide	0.250
aspartame	0.020 to 0.070*
polyplasdone XL10	0.100
sorbitol	0.300
microcrystalline cellulose	q.s.
mandarin orange flavor	0.050
magnesium stearate (for slugging)	0.015
magnesium stearate (for tableting)	0.015
Total Tablet Weight	2.100

*Amount of aspartame can vary with didanosine content.

EXAMPLE 6

Evaluation of the Comparative Bioavailability of Didanosine Administration of 375 mg Dose as a Solution, Chewable Tablet and Suspension

Assessment of bioavailabilities of didanosine from two new formulations, a chewable tablet and a suspension, relative to that of a citrate/phosphate buffer solution, was conducted in 18 male subjects who were seropositive for the Human Immunodeficiency Virus (HIV). This study was performed in six subjects at each of the three clinical sites using an open randomized three-way crossover design. Each subject received a single 375 mg didanosine oral dose after an overnight fast. There was a 7-day washout period between each treatment. Serial blood samples and the total urinary output over 12 hours were collected and assayed for intact didanosine by validated HPLC assays. Pharmacokinetic parameters were calculated using noncompartmental methods. The mean parameters are listed below.

Formulation	C _{MAX} (ng/ml)	T _{MAX} * (hr)	MRT(INF) (hr)	T-HALF (hr)	AUC(INF) (hr.ng/ml)	CLR (ml/min)	% UR
C/P Buffer	1901	0.68	1.77	1.36	2851	507	21.9
Chewable Tablet	2364	0.50	1.86	1.37	3315	455	23.0
Suspension	2651	0.50	1.80	1.39	3574	477	26.4

T_{MAX}*: median was reported.
C_{MAX} - highest observed plasma concentration of drug.
T_{MAX} - time elapsed to reach C_{MAX}.
T-HALF - the drug elimination half-life.
AUC(INF) - the area under the drug concentration vs time curve, extrapolated to infinity.
MRT(INF) - mean residence time in the body, extrapolated to infinity.
CLR - renal clearance of drug.
UR - total urinary recovery.

The rate of absorption and elimination of these three formulations were essentially the same, based on the values of T_{MAX}, MRT(INF) and T-HALF. The pharmacokinetic characteristics of didanosine remained unaltered regardless of the differences in formulation. The bioavailability estimates with 90% confidence limits for the chewable tablet relative to the citrate/phosphate buffer were 124% (106-135%) for C_{MAX} and 116% (108-125%) for AUC (INF). The bioavailability estimates with 90% confidence limits for the suspension relative to the citrate/phosphate buffer were 139% (121-154%) for C_{MAX} and 125% (117-134%) for AUC(INF). Based on the 90% confidence interval approach, the two new formulations were more bioavailable than the reference formulation, citrate/phosphate buffer.

EXAMPLE 7

Evaluation of the Comparative Bioavailability of Didanosine (2',3'-Dideoxyinosine, ddI) After Administration as a Solution and as a Chewable Tablet

The bioavailability of a chewable tablet formulation of didanosine relative to the reference formulation, a citrate/phosphate buffer sachet, was evaluated in 24 male patients seropositive for the Human Immunodeficiency Virus. Using a randomized crossover study design, a single 375 mg oral dose of the citrate/phosphate buffer sachet or a 300 mg dose of the chewable tablet (administered as 2x150 mg tablets) was given under fasting conditions. The alternate treatment was given 1 week later. Serial blood samples and the total urinary output were collected over a 12 hr interval after each dose. Plasma and urine samples were analyzed for didanosine using validated HPLC/UV methods. Concentration data were used to calculate pharmacokinetic parameters using noncompartmental methods. Mean (SD) values for key parameters are summarized below.

Formulation	C _{MAX} (ng/ml)	T _{MAX} * (hr)	MRT(INF) (hr)	T-HALF (hr)	AUC(INF) (hr.ng/ml)	CLR (ml/min)	% UR
Citrate/ Phosphate (584)	1595	0.75	2.35 (0.79)	1.76 (0.82)	2953 (838)	469 (160)	78.4 (26.7)
Chewable Tablet (548)	1628	0.50	2.18 (0.59)	1.73 (1.03)	2571 (773)	433 (169)	64.2 (25.4)

T_{MAX}*: median was reported.

There were no statistically significant sequence or period effects observed for any parameter, based on analysis of

variance results. The bioavailability assessment of the chewable tablet formulation of didanosine relative to the citrate/phosphate buffer was made on the basis of the two one-sided tests procedure. The point estimate and 90% confidence interval for C_{MAX} for the chewable tablet relative to the citrate/phosphate buffer sachet was 103% (95%, 112%). Corresponding values for AUC(INF) were 87% (81%, 93%). It is concluded that a 375 mg dose of didanosine, administered as the citrate/phosphate buffer is equivalent to a 300 mg dose of the chewable tablet.

EXAMPLE 8

Didanosine Chewable/Dispersible Buffered Tablets

The following tablet formulations are made using the procedures outlined above. These formulations have been utilized in clinical practice for efficacy studies. All of these tablets are qualitatively similar having the same physical parameters.

Ingredients	Strength					
	Placebo	25 mg	50 mg	100 mg	150 mg	200 mg
Didanosine activity	—	0.25	0.050	0.100	0.150	0.200
Calcium carbonate	0.550	0.550	0.550	0.550	0.550	0.550
Magnesium hydroxide	0.250	0.250	0.250	0.250	0.250	0.250
Aspartame	0.065	0.065	0.065	0.065	0.065	0.065
Sorbitol 30/60 DC	0.350	0.342	0.333	0.316	0.300	0.280
Microcrystalline cellulose	0.700	0.683	0.667	0.634	0.600	0.570
Polypasdone XL-10	0.100	0.100	0.100	0.100	0.100	0.100
Mandarin orange	0.050	0.050	0.050	0.050	0.050	0.050
Magnesium stearate (slugging)	0.015	0.015	0.015	0.015	0.015	0.015
Magnesium stearate (tableting)	0.020	0.020	0.020	0.020	0.020	0.020
Net Tablet weight(g)	2.100	2.100	2.100	2.100	2.100	2.100

As the tablet potency is increased with added didanosine, an equal reduction in the combined weight of microcrystalline cellulose and sorbitol is made to adjust for constant tablet weight. The ratio of microcrystalline cellulose to sorbitol is kept at a 2:1 ratio for all tablet strengths.

EXAMPLE 9

In-Vitro Testing of Stability of ddl (Stomach Degradation Model)

Didanosine (2,3-dideoxyinosine, dideoxyinosine, ddl) is an antiviral compound which demonstrates activity against the human immunodeficiency virus (HIV). This compound is presently indicated as a clinical agent for the treatment of Acquired Immune Deficiency Syndrome (AIDS). This compound is highly acid labile, but is quite stable in an alkaline environment {e.g., t_{90} (time period in which 90% of drug disappears) at 37° C. is <2 minutes at pH <3, 16 days at pH 7.4, and 509 days at pH 9.5 (1-3)}. While didanosine had been available previously in the form of a lyophilized intravenous dosage form, an oral dosage form is preferred for long-term therapy.

The acid labile nature of the didanosine bulk drug requires that the developed oral dosage form protect didanosine from acid degradation in the stomach after oral administration. The required degree of protection depends on the amount of residual acid in the stomach, the acid secretion rate, the gastric emptying rate for the dosage form, and the minimum gastric pH for acceptable didanosine stability.

Table 2 summarizes literature reporting human adult gastric secretion characteristics. These data suggest that the selected formulation should be capable of neutralizing a minimum of 27 mEq acid in an hour, assuming that the drug is administered on an empty stomach.

TABLE 2

Adult Human Stomach pH and Acid Secretion Characteristics*	
Stomach pH at Rest	1-2
Maximum Residual Acid at Rest	4 mEq
Maximum Secretion Rate at Rest	5 mEq/hour
Maximum Secretion Rate with Food	40 mEq/hour
Mean of Max. Secretion Rates at Rest and with Food	23 mEq/hour

*Modified from: L.R. Johnson, "Gastric Secretion," *Gastrointestinal Physiology*, L. R. Johnson, Ed., The C. V. Mosby Co., St. Louis, MO, 2nd ed. 1981, p. 70.

The literature indicates that, in most cases, solutions empty from the human stomach within ½ hour under fasting

conditions. In order to provide optimum bioavailability, the developed formulation should protect didanosine from an acidic environment for at least ½ hour.

Using the Acid Neutralization Rate Test (Example 1), solution stability of didanosine as a function of pH, in the range of pH 3-5, was determined at 37° C. The data are presented in FIG. 1. These data indicate a significant increase in the degradation rate as the solution pH was reduced. Less than 4% didanosine degradation was observed in ½ hour at pH 5. Thus, pH 5 was selected as the minimum pH which the formulation should maintain for at least ½ hour in the acid neutralization rate test described above.

The ideal buffer should maintain stomach pH above 5 for approximately one hour. However, the developed buffer should not raise the stomach pH much above 5, so as not to create a physiological pH imbalance in the gastrointestinal tract.

We claim:

1. A pharmaceutical composition for oral delivery of dideoxypurine nucleosides with improved bioavailability, the composition comprising;

from about 5 to 375 mg per dosing unit of a dideoxy purine nucleoside selected from the group consisting of 2',3'-dideoxyadenosine (ddA), 2',3'-dideoxyinosine (ddl), 2',3'-dideoxyguanosine (ddG), and individual pharmaceutically acceptable salts, prodrug esters, and hydrates thereof;

and about 800 to 2800 mg of a water-insoluble antacid buffering composition which contains a water insoluble antacid magnesium compound selected from the group consisting of magnesium carbonate, magnesium carbonate hydroxide, magnesium hydroxide, magnesium oxide, magnesium (tribasic) phosphate and magnesium trisilicate,

combined with a dihydroxyaluminum alkali metal carbonate or with calcium carbonate;

optionally containing a soluble citrate buffer;

and which optionally additionally contains binders, disintegrants, sweeteners, flavoring agents, and other pharmaceutically acceptable excipients;

with the proviso that the formulation does not act like a bulk laxative, cause constipation, or cause either physiological pH or electrolyte imbalances in the host following administration.

2. The pharmaceutical composition of claim 1 wherein the water-insoluble antacid buffering composition contains

one part of a water-insoluble antacid magnesium compound in combination with about 2 to 4 parts of a

15

dihydroxyaluminum alkali metal carbonate or with about 1.5 to 3 parts of calcium carbonate.

3. A chewable oral tablet formulation that may be chewed or dispersed in a liquid and swallowed, the tablet formulation containing the pharmaceutical composition of claim 1.

4. The composition of claim 1 containing a sweetening agent.

5. The composition of claim 4 wherein the sweetening agent is selected from the group consisting of aspartame, sorbitol and sucrose.

6. The composition of claim 1 containing a flavoring agent.

7. The composition of claim 1 containing a disintegrant.

8. The composition of claim 1 containing a binder.

9. The composition of claim 1 containing pharmaceutically acceptable excipients.

10. The composition of claim 1 wherein the dideoxy purine nucleoside is ddI.

11. The composition of claim 1 wherein the water-insoluble antacid buffering composition contains a dihydroxyaluminum alkali metal carbonate.

12. The composition of claim 11 wherein the water-insoluble antacid buffering composition contains dihydroxyaluminum sodium carbonate.

13. The composition of claim 1 wherein the water-insoluble antacid buffering composition contains calcium carbonate.

14. The composition of claim 1 wherein the water-insoluble antacid magnesium compound is magnesium hydroxide.

15. The composition of claim 1 containing -ddI, dihydroxyaluminum sodium carbonate, magnesium hydroxide, a soluble citrate antacid buffer, a sweetening agent, and a flavoring agent.

16. The composition of claim 1 containing -ddI, calcium carbonate, magnesium hydroxide, a sweetening agent, and a flavoring agent.

16

17. An oral tablet formulation containing the pharmaceutical composition of claim 15.

18. An oral tablet formulation containing the pharmaceutical composition of claim 16.

19. An oral powder formulation for dispersal in a liquid and containing the pharmaceutical composition of claim 1.

20. An oral powder formulation for dispersal in a liquid and containing the pharmaceutical composition of claim 15.

21. An oral powder formulation for dispersal in a liquid and containing the pharmaceutical composition of claim 16.

22. A chewable or dispersible tablet formulation comprising from about 5 to 375 mg of ddI; about 1.3 to 1.4 g of dihydroxyaluminum sodium carbonate; about 0.4 to 0.5 g of magnesium hydroxide; about 0.3 g of sodium citrate dihydrate; about 0.06 g aspartame and about 0.16 g sucrose; about 0.075 g tablet disintegrant, about 0.04 g silicon dioxide; about 0.02 g wintergreen flavor; about 0.05 g magnesium stearate; and sufficient microcrystalline cellulose to yield a tablet weighing about 3.0 g.

23. A chewable or dispersible tablet formulation comprising about 5 to 375 mg of ddI; about 0.5 to 0.6 g calcium carbonate; about 0.2 to 0.3 g magnesium hydroxide; about 0.06 g aspartame; about 0.08 g tablet disintegrant; about 0.02 g silicon dioxide; about 0.05 g orange flavor; about 0.02 g magnesium stearate and sufficient microcrystalline cellulose to yield a tablet weighing about 1.9 g.

24. A chewable or dispersible tablet formulation comprising about 5 to 375 mg of ddI; about 0.5 to 0.6 g calcium carbonate; about 0.2 to 0.3 g magnesium hydroxide; about 0.07 g aspartame; about 0.1 g tablet disintegrant; about 0.3 g sorbitol; about 0.05 g mandarin orange flavor; about 0.03 g magnesium stearate and sufficient microcrystalline cellulose to yield a tablet weighing about 2.1 g.

* * * * *

ANEXO 2



US 20020150617A1

(19) **United States**

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

(10) **Pub. No.: US 2002/0150617 A1**

(43) **Pub. Date: Oct. 17, 2002**

(54) **METHOD OF MAKING TABLETS AND
TABLET COMPOSITIONS PRODUCED
THEREFROM**

(75) **Inventors:** William J. Mergens, West Palm Beach,
FL (US); Kuei Tu Chang, Mountain
Lakes, NJ (US); Gerald T. Holly,
Delray Beach, FL (US)

Correspondence Address:
Woodcock Washburn LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103 (US)

(73) **Assignee:** Rexall Sundown, Inc.

(21) **Appl. No.:** 10/059,759

(22) **Filed:** Jan. 29, 2002

Related U.S. Application Data

(62) Division of application No. 09/639,780, filed on Aug.
16, 2000, now Pat. No. 6,358,526.

Publication Classification

(51) **Int. Cl.⁷** A61K 35/78; A61K 31/545;
A61K 31/715; A61K 9/20

(52) **U.S. Cl.** 424/465; 424/725; 514/54;
514/200; 424/730; 424/769;
424/728; 424/752; 424/766

(57) **ABSTRACT**

The present invention provides a method of making tablet compositions that are substantially free of excipients. The method includes forming a compactable granular mixture containing at least one compaction enhancing therapeutic compound, at least one other therapeutic compound that is different from the compaction enhancing therapeutic compound, and less than about 15 weight percent of a non-aesthetic excipient. The compactable granular mixture thus obtained is compressed to form a tablet composition. The present invention also provides tablet compositions produced by the methods of the present invention that are substantially free of excipients.

METHOD OF MAKING TABLETS AND TABLET COMPOSITIONS PRODUCED THEREFROM

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. application Ser. No. 09/639,780, filed Aug. 16, 2000, now allowed.

FIELD OF THE INVENTION

[0002] The present invention relates to a method for making tablets, and more particularly, relates to a method for making tablets that are substantially free of excipients, where at least one therapeutic compound in the tablet serves as a compaction enhancing agent for the tablet. The present invention also relates to tablet compositions produced by the methods of the present invention.

BACKGROUND OF THE INVENTION

[0003] Tablet compositions are commonly used to deliver therapeutic compounds to a patient such as a human or animal. By "tablet" as used herein, it is meant solid particles, containing or including therapeutic compounds, that are compressed under pressure into any desirable shape, such as a pill or caplet.

[0004] Typically, tablets contain other ingredients, hereinafter referred to as "excipients," that provide necessary physical or aesthetic properties to a tablet for delivery of the therapeutic compound. For example, with respect to physical properties, tablets generally need to have acceptable hardness, disintegration, dissolution rate for release of the therapeutic, friability, stability, and size to effectively deliver a therapeutic compound. With respect to aesthetics, it may be desirable for the tablet to contain additives that appeal to the human senses such as colorants, fragrances, texture modifiers, and/or flavorants. Specific types of excipients commonly used in tablet compositions include for example diluents, binders, lubricants, glidants, disintegrants, gelling agents, flavoring agents, and coloring agents. Many of these excipients are commonly added because the therapeutic compound alone may have poor compactability, and thus excipients are needed to achieve the desired tableting performance.

[0005] A problem, however, in using excipients, is that the tablet may become too large to ingest due to the amount of excipients needed to effectively formulate the tablet. A solution to this problem would be to reduce the amount of therapeutic compound and excipients to reduce the overall weight of the tablet, however, multiple tablets would then be needed to deliver the appropriate amount of therapeutic compound. Another problem in using excipients is that, particularly in nutraceuticals, they do not adequately compensate for low density of many herbal products and as such, are in many cases unsatisfactory solutions to tableting problems. Additionally, excipients often add cost to the tablet, and also may be objectionable to some consumers.

[0006] Tablet formulations in which it is especially desirable to reduce the amount of excipients are those used for the treatment of connective tissue to prevent, repair, or lessen ailments of the joints and cartilage tissue, such as observed with arthritis. For example, U.S. Pat. Nos. 5,364,845 and 5,587,363 both to Henderson ("Henderson") disclose thera-

peutic compositions for the treatment and repair of connective tissue containing amino sugars such as glucosamine, and glycosaminoglycans such as chondroitin. The compositions disclosed in Henderson are used in the form of a powder (for large animals) or capsule (for small animals). Additionally, it is known that these same compositions can be supplied in tablet form, if excipients are used. For example, the commercially available product called "Osteo-Bi-flex" supplied by Rexall Sundown, provides in tablet form a composition containing glucosamine, chondroitin sulfate, and excipients, where the excipients make up at least 23 wt % of the tablet formulation.

[0007] U.S. Pat. No. 5,843,919 to Burger discloses a composition and method for the treatment of arthritis where the composition contains one or more glucosamines and one or more omega-3-fatty acids. Although Burger discloses that a tablet can be prepared, it is apparent that excipients would be needed as Burger discloses that the glucosamine is preferably dissolved in an oil containing the omega-3-fatty acid.

[0008] Other compositions, which may optionally be in the form of tablets, for treating ailments of the joints and connective tissues are disclosed in for example U.S. Pat. Nos. 5,605,891 to Prino et al., 5,840,715 to Florio, and 5,849,336 to Aoyagi et al. These patents however, provide no specific example of useful tablet formulations.

[0009] Amino sugars and glycosaminoglycans have also been used in compositions for treating skin. For example, U.S. Pat. No. 5,804,594 to Murad discloses a composition for the prevention and treatment of skin conditions that contain a sugar compound, an antioxidant, an amino acid, a transition metal component, a catechin based preparation, a glucosamine and chondroitin. Although tablet formulations are disclosed, it is taught that such compositions need to be prepared in the presence of carriers.

[0010] With respect to other therapeutics, it is known that a therapeutic alone may be compressible, without excipients. For example, U.S. Pat. No. 5,079,007 to Putnam discloses an implant containing a crystalline salt of cephalosporin, an amorphous salt of cephalosporin and from 0 to 10 weight percent excipients. Putnam teaches that the crystalline and amorphous cephalosporin forms are compressible alone to form a tablet, and that the ratio of the two components are adjusted to obtain the desired release characteristics of the implant. Putnam thus does not describe a method for making a tablet where one therapeutic compound serves as a compaction enhancing agent for a different therapeutic compound.

[0011] Thus, it would be desirable to develop a method of making tablets and tablet compositions produced therefrom that are substantially free of excipients, where at least one of the therapeutic compounds is a compaction enhancing agent for the other therapeutic compound.

SUMMARY OF THE INVENTION

[0012] The present invention provides a method of making tablets that are substantially free of excipients. The method of the present invention includes forming a compactable granular mixture comprising (i) at least about 3 weight percent of a compaction enhancing therapeutic compound, (ii) at least one other therapeutic compound that is different

from the compaction enhancing therapeutic compound and (iii) less than about 15 weight percent of non-aesthetic excipients. The compactable granular mixture is compressed to form one or more tablets.

[0013] In a preferred embodiment of the present invention, the compaction enhancing therapeutic compound includes a glycosaminoglycan and the other therapeutic compound includes an amino sugar.

[0014] The present invention also provides a tablet composition containing from about 3 weight percent to about 99.5 weight percent of a compaction enhancing therapeutic compound; from about 0.5 weight percent to about 97 weight percent of at least one second therapeutic compound that is different from the compaction enhancing therapeutic compound; and less than about 15 weight percent excipients. The compaction enhancing therapeutic compound enhances the compaction of the second therapeutic compound and is preferably in intimate admixture with the second therapeutic compound.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The present invention provides a method of making tablets that are substantially free of excipients. The tablets produced by the method of the present invention contain at least two therapeutic compounds, where at least one of the therapeutic compounds serves as a compaction enhancing agent for the other therapeutic compound. By being able to provide tablets that are substantially free of excipients, smaller tablets and/or tablets containing greater amounts of therapeutic compounds can be produced. Thus, tablets can be provided that are more easily ingested due to the smaller size, and/or eliminating the need for taking multiple tablets to obtain a desired dosage of a therapeutic compound.

[0016] By "substantially free" of excipients it is meant that the tablet contains less than about 15 weight percent, more preferably less than about 8 weight percent, and most preferably less than about 2 weight percent excipients, based on the total weight of the tablet on a dry basis (i.e., excluding moisture as hereinafter defined). The term "excipient," as used herein refers to any additive, liquid or solid, present in the tablet that provides some non-therapeutic property to the tablet. For example, excipients are usually added to enhance mechanical or aesthetic properties in a tablet, or to dilute the therapeutic compound. As such, the term excipient, as used herein, does not include therapeutic compounds, or moisture, such as water or other solvent, that is used during the manufacture of the tablet, or is inherently present in one of the ingredients used to form the tablet. Common mechanical excipients include for example binding agents, lubricants, disintegrants, coating agents, gelling agents, glidants, absorbents, surfactants, antiadherents, or combinations thereof. Common aesthetic excipients include for example colorants, flavorants, or combinations thereof. Common excipients used to dilute the therapeutic compound include for example diluents, fillers, or combinations thereof. Preferably, the tablet contains less than about 15 wt %, more preferably less than 8 wt %, and most preferably less than about 2 wt % mechanical or diluting excipients (i.e., non-aesthetic excipients) based on the total weight of the tablet on a dry basis.

[0017] By "therapeutic compound" it is meant any substance used to treat (including prevent, diagnose, alleviate,

or cure) a malady, affliction, nutritional deficiency, disease or injury in a patient. The term "therapeutic compound" is also meant to include substances that are a supplement for improving the nutritional, physical, or emotional well being of a patient such as vitamins, minerals, or herbal based supplements. By "patient" it is meant a human and/or animal such as a mammal or reptile.

[0018] In the method of the present invention, a compactable granular mixture is formed containing (i) at least about 3 weight percent of a compaction enhancing therapeutic compound, (ii) at least one other therapeutic compound that is different from the compaction enhancing therapeutic compound and (iii) less than about 15 weight percent of non-aesthetic excipients. The compactable granular mixture is then compressed to form one or more tablets.

[0019] The compaction enhancing therapeutic compound is any therapeutic compound that enhances the compactability of the other therapeutic compound. By "enhances the compactability" it is meant that when the compaction enhancing therapeutic compound is mixed in the amounts (i.e., at least 3 weight percent) and manner (such as for example granulating, solvent dissolution and removal, or blending) as described herein with the other therapeutic compound, and optional lubricant, the granular mixture formed can be compressed into a tablet having acceptable friability (i.e., about 1% or less), and an increased hardness of at least about 10%, more preferably at least about 20%, and most preferably 50%, based on a tablet of the same weight, shape, and size, compressed under the same conditions, and not containing the compaction enhancing therapeutic compound. Hardness and friability can be determined by those techniques described hereinafter.

[0020] Preferably, the amount of compaction enhancing therapeutic compound in the tablet is at least about 3 weight percent to about 99.5 weight percent, more preferably from about 5 weight percent to about 50 weight percent and most preferably from about 5 weight percent to about 15 weight percent, based on the total tablet weight.

[0021] Examples of compaction enhancing therapeutic compounds include for example glycosaminoglycans such as heparin, dermatan sulfate, chondroitin, or sulodexide; herbal or botanical based extracts such as St. John's Wort extract, horse chestnut, ginseng, ginkgo biloba, kelp, grape seed extract; vitamins such as niacinamide ascorbate, and derivatives thereof; salt forms of minerals; anti-inflammatory agents such as naproxen; antibiotics such as cephalosporin; cholesterol lowering agents such as cholestyramine; pharmaceutically acceptable salts of any of the foregoing; or any combination thereof.

[0022] In a preferred embodiment of the present invention, the compaction enhancing therapeutic compound is a glycosaminoglycan such as chondroitin, derivatives of chondroitin, including pharmaceutically acceptable salts thereof; an herbal or botanical extract such as St. John's Wort extract, or grape seed extract; or combinations thereof.

[0023] The tablet also contains at least one other therapeutic compound that is different from the compaction enhancing therapeutic compound. This other therapeutic compound may be any therapeutic compound known to those skilled in the art. For example, the other therapeutic compound may be a compaction enhancing therapeutic

compound as previously described herein, or a compound that does not enhance compaction (i.e., a non-compaction enhancing therapeutic compound).

[0024] Examples of therapeutic compounds that may be used as the other therapeutic compound include anti-inflammatory agents; antibiotics; cholesterol lowering agents; antifungal agents; antineoplastic agents; analgesics; hormones; peptides; anticoagulation agents; circulatory drugs; antiangiinals; antituberculars; antivirals; narcotics; sedatives; diet products; nutritional supplements such as vitamins or minerals; herbal or botanical extracts; anti-smoking libido agents; amino acids, aminosugars; pharmaceutically acceptable salts or derivatives of any of the foregoing; or any combination thereof. Specific examples of vitamins and minerals useful as the other therapeutic compound include Vitamin C, dried powder forms of Vitamin A, Vitamin D, Vitamin E, Vitamin K, or beta carotene; B vitamins, such as thiamin, riboflavin, niacin, Vitamin B₆, Vitamin B₁₂, biotin, or folic acid; pantothenic acid, calcium, iron, zinc, iodine, magnesium, zinc, selenium, copper, manganese, chromium, molybdenum, potassium, boron, nickel, silicon, tin, vanadium; derivatives or salts of the foregoing; or combinations thereof. Examples of herbal or botanical extracts useful as the other therapeutic compound in the present invention include St. John's Wort extract, horse chestnut, ginseng, ginkgo biloba, kelp, grape seed extract or combinations thereof.

[0025] In a preferred embodiment of the present invention, the other therapeutic compound is a therapeutic compound that does not enhance the compactability of another therapeutic compound. Examples of therapeutic compounds that do not enhance the compactability of a therapeutic compound include for example aminosugars such as glucosamine, including derivatives or pharmaceutically acceptable salts thereof, such as N-acetyl glucosamine sulfate, glucosamine hydrochloride, or glucosamine sulfate; certain vitamins and derivatives or salts thereof such as Vitamin C (e.g., ascorbic acid), Vitamin B (e.g., thiamin hydrochloride, thiamin mononitrate, Vitamin B₆, Vitamin B₁₂, niacin, biotin, folic acid, pantothenic acid), dried powder forms of Vitamin A, Vitamin D, Vitamin E, Vitamin K, or beta carotene; certain amino acids such as arginine and derivatives thereof or salts thereof; or combinations thereof.

[0026] Preferably, the other therapeutic compound is present in the tablet in an amount equal to or less than about 97 weight percent, more preferably from about 0.5 weight percent to about 95 weight percent and most preferably from about 10 weight percent to about 95 weight percent, based on the total tablet weight.

[0027] With respect to the compactability properties of a therapeutic compound, one skilled in the art will recognize that a therapeutic compound in one form may enhance the compactability of another therapeutic compound and/or be compactable, but in another form (such as crystalline) may not enhance compactability of a therapeutic compound. As such it is possible that a therapeutic compound in two different forms could be formulated in a single tablet that is substantially free of excipients. However, the tablet should contain at least one therapeutic compound that is chemically different from the compaction enhancing therapeutic compound. For example, the tablet may contain two different compaction enhancing therapeutic compounds and no other

therapeutic compounds; one compaction enhancing therapeutic compound and one or more non-compaction enhancing therapeutic compounds; or one or more compaction enhancing therapeutic compound and one or more non-compaction enhancing therapeutic compounds.

[0028] The compaction enhancing therapeutic compound and the other therapeutic compound are formed into a compactable granular mixture. By "compactable," it is meant that the granular mixture is capable of forming a 500 mg sized round tablet having a diameter of 7/16" (standard concave) at a compaction pressure of greater than about 1000 lbs and having a hardness of at least about 5 Strong Cobb (SC) and a friability of less than about 1%. Preferably, the compactable granular mixture will be freely flowable for tableting. Preferably, the compactable granular mixture will have a particle size distribution of 95 percent by weight of the particles passing through a 20 mesh screen and less than 50% by weight of the particles passing through a 100 mesh screen (standard US mesh size).

[0029] One skilled in the art will recognize that there are various ways to form a compactable granular mixture. Any method may be used for combining the therapeutic compounds and other desired additives (e.g., excipients) that results in a compactable granular mixture. For example, a compactable granular mixture may be formed by blending the compaction enhancing therapeutic compound, the other therapeutic compound, and any other additive as a dry blend. A compactable granular mixture may also be formed by granulating a mixture containing the compaction enhancing therapeutic compound and other therapeutic compound. A compactable granular mixture may also be formed by at least partially or completely dissolving the compaction enhancing therapeutic compound and other therapeutic compound in a suitable liquid, followed by removal of the liquid. It may also be necessary, as hereinafter described, to subsequently process the mixture formed (e.g. pulverize, agglomerate) after combining the therapeutic compounds to form the compactable granular mixture.

[0030] One skilled in the art will recognize that the desired method chosen for forming a compactable granular mixture will depend upon, for example, the selection of the compaction enhancing therapeutic compound, the other therapeutic compound, and any other desired additive. For example, as explained in further detail hereinafter, it may be necessary, based on the selected therapeutic compounds, to form granules containing an intimate admixture of at least a portion of the compaction enhancing therapeutic compound and at least a portion of the other therapeutic compound to form a compactable granular mixture. However, it may also be possible that certain compaction enhancing therapeutic compounds may simply be mixed with the other therapeutic compound to form a compactable granular mixture.

[0031] By "intimate admixture," it is meant that the compaction enhancing therapeutic compound is uniformly admixed at a molecular level with the other therapeutic compound (e.g., in the case of at least partially dissolving both therapeutic compounds in a fluid, and removing the fluid), and/or admixed in a manner so that discrete particles containing the compaction enhancing therapeutic compound or a solid film containing the compaction enhancing therapeutic compound are in at least partial contact with the surfaces of the particles containing the other therapeutic

compound. In a preferred embodiment, the compaction enhancing therapeutic compound is at least partially coated as a solid film onto the surfaces of the other therapeutic compound.

[0032] There are various ways in which granules containing an intimate admixture of the compaction enhancing therapeutic compound and the other therapeutic compound may be formed. For example, granules of an intimate admixture of the therapeutic compounds may be prepared by wet granulating or solvent dissolution and removal process methods. In some circumstances, dry granulating may be used to form granules containing an intimate admixture of the therapeutic compounds. "Granulating" as used herein refers to a process where two or more smaller particles are combined to form larger granule particles through such processes as extrusion, compaction, fluid-bed granulation, or tumbling. "Solvent dissolution and removal" as used herein refers to a process where solids are at least partially dissolved in a liquid, and then the liquid is removed to form a granular mixture (e.g., spray drying).

[0033] One skilled in the art will recognize that there are various ways to wet granulate the therapeutic compounds. Typically, the therapeutic compounds will be mixed in the presence of a granulating fluid, and wet granules containing an intimate admixture of the therapeutic compounds will be formed simultaneously with mixing, and/or subsequently through additional means. The wet granules containing the therapeutic compounds are then preferably dried and pulverized to a suitable particle size for tabletting.

[0034] There are various ways in which the granulating fluid may be added to the therapeutic compounds. For example, a dry blend may be formed containing the therapeutic compounds, and the granulating fluid may be added to the dry blend to form a wetted mixture of therapeutic particles. Alternately, one or more compaction enhancing therapeutic compounds may be dissolved or dispersed in the granulating fluid that is then added (e.g., by spraying) to a dry blend containing the other therapeutic compound to form a wetted mixture of the therapeutic particles.

[0035] One skilled in the art will also recognize that there are various ways in which to granulate the wetted mixture of therapeutic particles. For example, granules may be simultaneously formed while adding the granulating fluid to the therapeutic compound(s) with mixing, such as tumbling, vibrating or shaking. Also, granules may be formed by extruding the wetted mixture of therapeutic granules and/or particles through a die or screen to form larger granules in various shapes such as noodles, pellets, briquettes, spheres, or combinations thereof.

[0036] Suitable equipment for wet granulating is disclosed in for example Chemical Engineers' Handbook, by Perry and Chilton, fifth edition, published by McGraw-Hill Inc., 1973, Chapters 8 and 19, the disclosure of which is hereby incorporated by reference in its entirety. In a preferred embodiment of the present invention, continuous granulation equipment is used such as a single screw or twin screw extruder. A preferred extruder is an extruder supplied by Rietz Manufacturing Company. Alternatively, batch equipment designed for the blending both solids and liquids may be used such as for example cone and screw mixers, double arm kneaders, twin blade conical mixers, planetary mixers, helical ribbon blade mixers, conical blenders, or combinations thereof.

[0037] The granulating fluid used for wet granulating may be water or any biocompatible solvent that is effective in forming granules containing an intimate admixture of the therapeutic compounds. In a preferred embodiment of the present invention, the granulating fluid is chosen so that the compaction enhancing therapeutic compound is at least partially soluble and more preferably completely soluble in the granulating fluid. Preferably also, the granulating fluid is selected so that the other therapeutic is at least partially insoluble.

[0038] The amount of granulating fluid added during granulation to form the wetted mixture of therapeutic particles will depend on such factors as the processing equipment chosen, the types of therapeutic compounds selected, the particle size of the therapeutic compounds, and length of processing time. Typically however the amount of fluid will be from about 5 weight percent to about 30 weight percent, and more preferably from about 8 weight percent to about 15 weight percent, based on the total weight of solids being granulated.

[0039] Examples of fluids that may be used include water, biocompatible organic solvents such as C_1 to C_4 alkyl alcohols, such as methanol, ethanol, n-propanol, isopropanol, or butanol; ethers such as alkoxyated ethers, alkyl ethers, diether, triethers, oligo ethers, polyethers, or cyclic ethers; ketones such as acetone or methyl ethyl ketone; alkyl acetates such as ethyl acetate; alkanes, such as C_5 to C_8 aliphatic alkanes such as hexane or heptane; cyclic hydrocarbons such as C_5 to C_8 cyclic hydrocarbons such as cyclopentane or cyclohexane; aromatic hydrocarbons and derivatives thereof such as toluene; or combinations thereof.

[0040] It is also possible to form the granulate mixture using a supercritical fluid as the granulating fluid. A supercritical fluid exists at conditions where its liquid and gaseous states are indistinguishable from one another. The critical temperature of a fluid is the temperature above which that fluid cannot be liquified by an increase in pressure. The critical pressure of a fluid is the pressure of the fluid at its critical temperature. Examples of useful supercritical fluids include carbon dioxide, or mixtures of carbon dioxide and aliphatic or cyclic alkanes.

[0041] The temperature and pressure at which wet granulation is carried out will depend on the therapeutic compounds and granulating fluid chosen. Preferably, when using water, wet granulation will be carried out at a temperature of from about 22° C. to about 37° C., and more preferably from about 22° C. to about 30° C. Typical granulation pressures through the die range from about atmospheric pressure to several thousand pounds per square inch (psi). In the case of using a supercritical fluid, wet granulation would be carried out at a temperature and pressure at which the fluid exists in a supercritical state.

[0042] Following wet granulation, at least a portion of the granulating fluid is removed from the wet granulate mixture to form a dry granulate mixture. The amount of fluid removed will depend on such factors as the total amount of granulating fluid added, selection of the therapeutic compounds, particle sizes of the therapeutic compounds, and the solubilities of the therapeutic compounds in the granulating fluid. Preferably, at least about 50 weight percent, and more preferably from about 80 weight percent to about 98 weight percent of the added granulating fluid in the wet granulate

mixture is removed to form a dry granulate mixture. The drying temperature is preferably chosen to efficiently remove the granulating fluid without degrading the therapeutic compounds in the granulate mixture.

[0043] A granulate mixture may also be formed by at least partially dissolving, and more preferably completely dissolving the compaction enhancing therapeutic compound and the other therapeutic compound in a liquid, and removing the liquid by any suitable technique to form granules containing the therapeutic compounds in intimate admixture. The selection and amount of liquid used will depend on the solubilities of the therapeutic compounds.

[0044] Examples of suitable liquids include water, bio-compatible organic solvents such as C_1 to C_4 alkyl alcohols, such as methanol, ethanol, n-propanol, isopropanol, or butanol; ethers such as alkoxyated ethers, alkyl ethers, diether, triethers, oligo ethers, polyethers, or cyclic ethers; ketones such as acetone or methyl ethyl ketone; alkyl acetates such as ethyl acetate; alkanes, such as C_5 to C_8 aliphatic alkanes such as hexane or heptane; cyclic hydrocarbons such as C_5 to C_6 cyclic hydrocarbons such as cyclopentane or cyclohexane; aromatic hydrocarbons and derivatives thereof such as toluene; or combinations thereof.

[0045] Any technique known to those skilled in the art for removing the liquid from the therapeutic compound may be used such as continuous dryers (e.g., spray, fluid bed, tube, Witte or tunnel dryers), or batch dryers (e.g., rotary, pan, vacuum, or microwave dryers). In a preferred embodiment, the liquid is removed by a spray dryer. The drying conditions (e.g., temperature and pressure) will depend on the selection of liquid and therapeutic compounds, and should be chosen so as to not degrade the therapeutic compounds.

[0046] It is also possible, depending on the compaction enhancing therapeutic compound chosen, and possibly the level of moisture present in the mixture being granulated, that dry granulation can be used to form granules containing an intimate admixture of the compaction enhancing therapeutic compound and other therapeutic compound. "Dry granulation" refers to a granulation process where no external fluid is added during processing. In such an embodiment, preferably the therapeutic compounds being granulated contain a total of at least about 4 wt % moisture, more preferably from about 5 wt % to about 15 wt % moisture, and most preferably from about 6 wt % to about 10 wt % moisture, based on the total weight of the therapeutic compounds. Such moisture is preferably inherently present in the therapeutic compounds as supplied. Preferably, the moisture present is water. It is believed that having some moisture in the therapeutic compounds aids in achieving an intimate admixture during dry granulation.

[0047] Any technique known to those skilled in the art may be used for dry granulating that promotes the formation of an intimate admixture of the therapeutic compounds. For example, dry granulation may be accomplished by admixing the compaction enhancing therapeutic compound and other therapeutic compound in a suitable piece of mixing equipment, and/or using compaction equipment, such as a roll press, to compact the dry blend into a desired shape to form an intimate admixture. In a preferred embodiment, dry granulation is carried out using a Chilsonator™ press.

[0048] The temperature and pressure at which dry granulation is carried out will depend on the therapeutic com-

pounds chosen. Preferably, dry granulation will be carried out at a temperature of from about ambient to about 45° C., and more preferably from about 20° C. to about 30° C.

[0049] Although it is preferred to form granules containing an intimate admixture of the compaction enhancing therapeutic compound and other therapeutic compound, it may be possible to simply blend the therapeutic compounds to form a compactable granular mixture. Any suitable equipment may be used to blend the therapeutic compounds including continuous or batch mixers suitable for mixing solids such as cone and screw mixers, twin blade conical mixers, planetary mixers, helical ribbon blade mixers, conical blenders.

[0050] To obtain a freely flowable compactable granular mixture, it may be desirable to further process the mixture containing the compaction enhancing therapeutic compound and other therapeutic compound prior to compressing into tablets. For example, when the therapeutic compounds are combined using wet or dry granulating methods, it may be desirable to further reduce the particle size of the coarse granules (e.g., noodles, pellets) obtained from such methods. Any suitable particle size reduction technique may be used that will provide the desired granulate particle size. Examples of suitable particle size reduction equipment is disclosed in for example Chemical Engineers' Handbook, by Perry and Chilton, fifth edition, published by McGraw-Hill Inc., 1973, Chapter 8, the disclosure of which is incorporated by reference in its entirety. Preferred particle size reduction equipment includes a comil; a Fitz mill manufactured by the Fitzpatrick Company; delumpers; hammer mills or combinations thereof.

[0051] In the case of using solvent dissolution and removal techniques as previously described herein (e.g., spray drying), it may be desired to further increase the particle size of the granulate mixture. Any method known to those skilled in the art may be used to further agglomerate the granulate mixture, such as the wet granulation and dry granulation techniques previously described herein. Also, fluid beds, spheronization equipment, or rotating pans may be used to agglomerate.

[0052] The compactable granular mixture that is compressed may contain low levels of excipients (i.e., additives) as hereinafter described, or other therapeutic compounds, that are added after combining the at least one compaction enhancing therapeutic compound and other therapeutic compound by such techniques as granulation. In a preferred embodiment of the present invention, at least a portion of the compaction enhancing therapeutic compound is wet granulated with at least a portion of the other therapeutic compound. Preferably, at least 5 weight percent, and more preferably at least 10 weight percent of the compaction enhancing therapeutic compound is granulated with at least 15 weight percent, and more preferably at least 30 weight percent of the other therapeutic compound. The remaining therapeutic compounds may be, for example, simply admixed after granulation.

[0053] In a preferred embodiment, the compactable granular mixture is prepared by wet granulating all the compaction enhancing therapeutic compound and all the other therapeutic compound by adding water in a high shear granulator or extruder, and drying the granules formed in a fluid-bed dryer, tunnel dryer, or tray dryer to obtain granules

containing from about 0.5 weight percent to about 10 weight percent moisture, based on the total weight of the granules. The granules are then preferably milled through a Fitz mill equipped with a 20 U.S. standard mesh screen.

[0054] The compactable granular mixture formed is preferably in a freely flowable form for feeding into compression equipment to form tablets. Preferably, the flow of the compactable granular mixture is from about 5 to about 30 seconds through a funnel having an upper opening diameter of about 8.89 cm, a lower opening of about 1.11 cm, and a height from upper opening to lower opening of about 20.32 cm. Also preferably, the particle size distribution is such that 95 percent by weight of the particles pass through a 20 mesh screen and less than 50% by weight of the particles pass through a 100 mesh screen (standard US mesh size). Also, preferably, any fluids used in forming the compactable granular mixture are removed so that the mixture contains less than about 15 weight percent, more preferably less than about 10 weight percent, and most preferably less than about 8 weight percent moisture based on the total weight of the therapeutic compound.

[0055] In addition to the therapeutic compounds, the compactable granular mixture that is compressed to form a tablet may contain additives (i.e., excipients) in an amount of less than about 15 weight percent, based on the total weight of the compactable granular mixture (dry basis). Examples of additives that may be included in the compactable granular mixture are non-therapeutic binding agents, lubricants, diluents, disintegrants, glidants, absorbents, antiadherents, surfactants, coating agents, gelling agents, colorants, flavorants, or combinations thereof. One skilled in the art will recognize that some additives may serve a dual purpose in the tablet composition. For example, many cellulose containing compounds can serve as a binding agent, and diluent or disintegrant at high levels.

[0056] The additives may be added in any manner that provides a uniform dispersion of the additives in the compactable granular mixture that is compressed into tablets. For example, the additives may be added to one or more of the therapeutic compounds prior to, or during combining of the therapeutic compounds. For example, the additive may be mixed with the therapeutic compounds to form a dry blend prior to wet granulation or dry granulation. The additive may also be dissolved or dispersed in a liquid containing the therapeutic compounds prior to a solvent dissolution and removal process, or in a granulating fluid, optionally containing the compaction enhancing therapeutic compound prior to wet granulating. In such procedures, the additive is preferably part of the granule particles making up the granulate mixture. The additives may also be added subsequent to forming granules of therapeutic particles provided that the additive is uniformly dispersed in the compactable granular mixture prior to forming the tablet composition. For example, the additive may be blended as is with the granules of therapeutic compounds or may be dissolved or dispersed in a biocompatible liquid and applied to the granules of therapeutic compounds.

[0057] The preferred method of adding the additive will depend upon the additive. For example, binding agents, such as polyvinylpyrrolidone (PVP) or hydroxypropylmethylcellulose are preferably added prior to, or during the forming of the granules containing the therapeutic compounds, so that

the additive is part of the granule formed. Dry binding agents, such as microcrystalline cellulose, are preferably added subsequent to forming granules of the therapeutic compound. Also, for example, non-compaction enhancing therapeutic compounds, such as glucosamine, can be granulated with 5 wt % polyvinylpyrrolidone, and mixed with a compaction enhancing therapeutic compound such as chondroitin that has a moisture content above 7 wt %. Some specific examples of additives useful in the method of the present invention are described below.

[0058] In a preferred embodiment of the present invention, the compactable granular mixture may contain less than about 10 weight percent, more preferably less than about 5 weight percent and most preferably from 0 to about 3 weight percent non-therapeutic binding agents based on the total weight of the compactable granular mixture (dry basis). Any binding agent that imparts cohesive strength to granules containing the therapeutic compounds or the compactable granular mixture may be used. Examples of non-therapeutic binding agents useful in the present invention include for example polyvinyl pyrrolidone; modified or unmodified starch; cellulose containing compounds such as hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), carboxymethylcellulose (CMC), methylcellulose or ethylcellulose; polyalkyleneglycols such as polyethyleneglycol or polypropyleneglycol; gelatin; acacia gum; guar gum; sodium alginate; amylopectin, sorbitol; glucose; dextrin or combinations thereof. Preferred binding agents are polyvinyl pyrrolidone, HPMC, lower substituted HPC or combinations thereof.

[0059] The compactable granular mixture may also contain one or more lubricants to inhibit sticking of the granules or compactable granular mixture during processing. Preferably, the lubricant is present in the compactable granular mixture in an amount of from 0 weight percent to about 5.0 weight percent, and more preferably from about 0 to about 2.0 weight percent based on the total weight of the compactable granular mixture (dry basis). Examples of suitable lubricants include stearates such as stearic acid, palmitate, magnesium stearate, zinc stearate or calcium stearate; talc; hydrogenated vegetable oil; hydrogenated castor oil; liquid paraffin; surfactant; or combinations thereof.

[0060] The compactable granular mixture may also contain diluents that increase the bulk of the tablet. Examples of diluents useful in the present invention include for example sugars such as mannitol, sorbitol, or xylitol, lactose, dextrose, fructose, amylose, or sucrose; microcrystalline cellulose; ethyl cellulose; modified or unmodified starch; clays such as kaolin, alkaline earth metal carbonates, phosphates or sulfates such as calcium carbonate, magnesium carbonate, calcium phosphate, (e.g. di and tri basic calcium phosphate), calcium sulfate, or barium sulfate; magnesium trisilicate; aluminum hydroxide; or combinations thereof. The diluents preferably make up from 0 to about 15 weight percent, and more preferably 0 to about 10 weight percent of the compactable granular mixture (dry basis).

[0061] Disintegrants are used to facilitate the break-up of the tablet, after the tablet is administered to the patient. Preferably, the compactable granular mixture will contain from 0 to about 5 weight percent and more preferably from about 0.5 weight percent to about 2.0 weight percent disintegrants based on the total weight of the compactable

granular mixture (dry basis). Examples of disintegrants useful in the present invention include modified or unmodified starches such as corn starch, potato starch, or wheat starch; croscarmellose, clays; cross-linked polyvinyl pyrrolidone; cellulose containing compounds, gums, algin, surfactant, HPC, or combinations thereof.

[0062] Coating agents are applied to the surfaces of the formed tablet and provide, for example, reduced friability and ease of swallowability. Preferably, the amount coating agent is from about 0.5 wt % to about 6.0 wt % and more preferably from about 1.0 wt % to about 5.0 wt % based on the total weight of the compactable granular mixture (dry basis). Examples of suitable coating agents include cellulose containing compounds such as hydroxypropylmethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, methylcellulose or ethylcellulose; polyalkyleneglycols such as polyethyleneglycol or polypropyleneglycol; or combinations thereof.

[0063] The compactable granular mixture may also contain wetting agents, colorants, flavorants or combinations thereof. These additives preferably make-up from about 0.1 weight percent to about 10 weight percent, and more preferably from about 0.3 weight percent to about 5 weight percent of the compactable granular mixture (dry basis). Examples of suitable wetting agents include sodium dodecyl sulphate, sodium lauryl sulphate, polyoxyethylene sorbitan fatty acid esters (e.g., Tween™ compounds), polyoxyethylene stearates, sorbitan fatty acid esters or combinations thereof. Suitable colorants include for example red beet powder, ferric oxides, FD & C dyes or combinations thereof. Flavoring agents useful in the present invention include for example fruit flavors, or sweeteners such as sodium saccharin, aspartame, confectionary sugar, sorbitol, sucrose, xylitol, or combinations thereof.

[0064] The compactable granular mixture thus prepared in accordance with the method of the present invention is compressed into a tablet according to any technique known to those skilled in the art. For example, in compacting the compactable granular mixture, the compactable granular mixture can be added to a die, and compressed into a tablet having the desired shape and weight. Prior to adding the compactable granular mixture to the die, it may be desirable to apply an external lubricant to the wall of the die. Examples of external lubricants useful in the method of the present invention include talc; starch; stearates such as magnesium stearate; hydrogenated vegetable oil; surfactant or combinations thereof.

[0065] Preferably the compactable granular mixture is compressed at any suitable pressure and temperature to form a tablet having the desired properties such as strength, hardness, disintegration and release of the therapeutic compounds upon administration. Preferably, the compaction conditions are such that there is no degradation of the therapeutic compounds. Also, preferably, the compaction conditions are below the melting points of the therapeutic compounds to prevent lower tablet hardness or other tabletting process problems (e.g. glazing). Typical compaction pressures range from about 1000 lbs to about 10,000 lbs, and more preferably from about 4,000 lbs to about 8,000 lbs, where lbs is pounds force. Typical compaction temperatures range from about 15° C. to about 6020 C. and more preferably from about 20° C. to about 40° C.

[0066] The tablets thus produced may be further processed as desired. For example, the tablet may be coated according to any technique known to those skilled in the art. Suitable coatings include those compounds previously described as being useful as coating agents for the compactable granular mixture. The tablets may also be enteric or regularly polished with such compounds as Carnuba wax.

[0067] The tablet compositions useful in the present invention contain preferably from about 3 weight percent to about 99.5 weight percent, more preferably from about 5 weight percent to about 50 weight percent, and most preferably from about 5 weight percent to about 15 weight percent of at least one compaction enhancing therapeutic compound, based on the total weight of the tablet composition. The tablets also preferably contain from about 0.5 weight percent to about 97 weight percent, more preferably from about 10 weight percent to about 95 weight percent, and most preferably from about 40 weight percent to about 95 weight percent of at least one second therapeutic compound that is different from the compaction enhancing therapeutic compound, based on the total weight of the tablet composition. The compaction enhancing therapeutic compound is preferably in intimate admixture with the second therapeutic compound. More preferably, the compaction enhancing therapeutic compound at least partially coats particles of the second therapeutic compound.

[0068] The tablet composition thus produced also preferably contains less than about 15 weight percent, more preferably less than about 8 weight percent, and most preferably less than about 2 weight percent excipients, based on the total weight of the tablet composition (dry basis). The excipients may be any of the additives previously described herein that are present in the compactable granular mixture and in the amounts previously described for the compactable granular mixture. Preferably, excipients that serve as a lubricant are present in the tablet composition in an amount of no more than 0.5 weight percent based on the total weight of the tablet composition.

[0069] The overall weight of the tablet ranges from about 100 mg to about 2000 mg, and more preferably from about 450 mg to about 1600 mg.

[0070] One skilled in the art will recognize that the tablet compositions made in accordance with the methods of the present invention can be used for a variety of purposes. For example, the tablets may be formulated to provide treatment of connective tissue, such as to prevent, repair, or lessen ailments of the joints and cartilage tissue, such as observed with arthritis. The tablet compositions may also be prepared to treat ailments of the skin such as hardening, roughening, aging, or wrinkling of the skin. The tablet compositions may also be prepared to provide to a patient nutritional supplements of vitamins, minerals, antioxidants, or to function as an appetite suppressant, analgesic, anti-smoking libido, or combinations thereof. The tablet compositions may also be prepared to enhance the emotional well being of a patient through for example herbal based extracts. The tablet compositions of the present invention may also be prepared to treat ailments such as viral, fungal, or bacterial infections, diseases, or injuries to the body.

[0071] There are many advantages to the tablet compositions prepared in accordance with the methods of the present invention. For example, by the tablet compositions being

substantially free of excipients, smaller (in weight and volume) tablets can be prepared containing the same amount of therapeutic compound. By decreasing the excipients present in the tablet, the tablets prepared according to the method of the present invention can be more easily ingested, and/or formulated to contain more therapeutic compound(s) in a single tablet. By being able to increase the amount of therapeutic compounds in a single tablet, one reduces the need to ingest multiple tablets at a single time and/or multiple doses of the same product. Additionally, the reduction of excipients in tablets is beneficial to hyper-allergic patients and also has a very positive effect on diurnal consumer compliance.

[0072] In a preferred embodiment of the present invention, the tablet composition made in accordance with the methods of the present invention contains from about weight percent 3 to about 80 weight percent, and more preferably from about 30 to about 60 weight percent of at least one glycosaminoglycan; from about 3 weight percent to about 95 weight percent, and more preferably from about 5 weight percent to about 70 weight percent of at least one amino sugar; and less than about 2 weight percent, and more preferably less than about 0.5 weight percent of excipients based on the total weight of the tablet (dry basis). Preferably, the amino sugar is glucosamine, or a derivative or pharmaceutically acceptable salt thereof and the glycosaminoglycan is chondroitin or a derivative or pharmaceutically acceptable salt thereof. In this preferred embodiment, other therapeutic compounds may be present in the tablet composition such as manganese ascorbate, sodium ascorbate, calcium ascorbate, Vitamin C (i.e., ascorbic acid), dried powder forms of Vitamin A, Vitamin D, Vitamin E, Vitamin K, or beta carotene; vitamin B₆, niacin, phosphorous containing salts, zinc containing salts, copper containing salts, calcium containing salts such as calcium citrate, calcium carbonate, oyster shell, magnesium, manganese sulfate, boron, estrogen(s), or combinations thereof. Preferably calcium is present in an amount of from about 7 weight percent to about 15 weight percent; and the vitamin C is preferably present in an amount of from about 1 weight percent to about 10 weight percent, based on the total weight of the tablet composition (dry basis).

[0073] Also preferably in this embodiment, the overall weight of the tablet ranges from about 100 mg to about 2000 mg, and more preferably from about 500 mg to about 2000 mg. The aminosugar is preferably present in an amount of from about 250 mg to about 1000 mg, and the glycosaminoglycan is preferably present in an amount of from about 200 mg to about 1000 mg. Any excipients are preferably present in an amount of less than about 50 mg.

[0074] The above preferred tablet composition containing an aminosugar and glycosaminoglycan is particularly useful for the treatment of connective tissues. Other preferred compositions that can be formed into a tablet in accordance with the method of the present invention are those compositions disclosed in for example U.S. Pat. Nos. 5,364,845 and 5,587,363 both to Henderson, the disclosures of which are hereby incorporated by reference in their entireties.

EXAMPLES

[0075] Some embodiments of the present invention will now be described in detail in the following Examples. Tablet

compositions were prepared in accordance with the method of the present invention and evaluated for various properties. The following test procedures were used in the Examples for evaluating tablet properties.

TABLE 1

Test Methods for Properties Measured and Abbreviations Used in Examples			
Property	Units	Method	Equipment
Hardness	Strong-Cobb	—	Key International Hardness Tester
Disintegration Time (DT)	Minutes (min)	USP ¹ 2040	VanderCamp-disintegration Apparatus
Ejection Force (EJ Force)	Pounds (lbs)	—	B ₃ B 16 station Instrumented Tablet Press
Weight variation (Wt. Var.)	%	USP 2091	Mettler 3 place balance
Friability (Friab.)	%	USP 1216	Tablet Friability Apparatus

¹USP refers to the United States Pharmacopeia, Vol. USP XXIV/NF XIX, published by US Pharmacopeia Convention Incorporated located in Rockville, MD, 1999. The number following "USP" refers to the section in which the test method is found.

[0076] In Table 1 above, weight variation is expressed as the percent standard deviation in tablet weight for 20 tablets based on the average tablet weight. Friability is expressed as the percent of the tablet weight loss that was friable in the friabilator after 100 rotations (20 tablets).

[0077] Unless otherwise indicated in the Examples, the chondroitin used was chondroitin sulfate sodium salt obtained from Tomen America located in New York, N.Y. The chondroitin had an active ingredient content of 85 weight percent, and loss on drying (LOD) of 9.25 weight percent based on the total weight. Unless otherwise indicated in the Examples, the glucosamine used was glucosamine HCl obtained from Nutratech Corp., located in Fairfield, N.J. The glucosamine had an active ingredient content of 99 weight percent and was milled prior to use in a Fitz mill having a 60 mesh screen. Magnesium stearate was obtained from Mallinkrodt located in St. Louis, Mo. Any reference in the examples to mesh screen size refers to U.S. standard mesh size.

Comparative Example 1

[0078] Tablets containing 470.59 mg of chondroitin, 505.05 mg glucosamine and 4.90 mg of magnesium stearate were prepared using either milled glucosamine as previously described or unmilled glucosamine. The unmilled glucosamine had a particle size distribution of 95 wt % of the particles being smaller than a 20 mesh screen size, and 50 wt % of the particles being greater than a 60 mesh screen size.

[0079] The tablets were prepared by mixing the proper amounts of chondroitin and glucosamine in a blender for 15 minutes to form a dry blend. The magnesium stearate was separately mixed with an equal amount of the dry blend and passed through a 30 mesh screen to form a magnesium stearate mixture. This magnesium stearate mixture was then added to the dry blend and mixed for an additional 5 minutes. Tablets were then prepared using a Manesty 16 station B₃B instrument equipped with an instrumentation

package, supplied by SMI Corp., capable of continuously recording compression speed, compression force, and ejection force.

[0080] The tableting conditions were as follows:

Tableting speed	40 revolutions per minute (RPM)
Compression force	varied
Tablet punches	5/16" x 3/4" caplet, B tooling
Tablet weight	989.24 mg

[0081] For tablets prepared using milled glucosamine, a tablet hardness of 10 Strong-Cobb was achieved at a compaction pressure of 5500 lbs. For tablets prepared using unmilled glucosamine a hardness of 1.5 Strong-Cobb was obtained at a compaction pressure of 3000 lbs. For both tablets, at a compaction pressure of 4000 lbs and greater, capping was observed.

Comparative Example 2

[0082] To a blender was added 470.59 parts by weight chondroitin, 505.05 parts by weight glucosamine, and 35.35 parts by weight red beet powder to form a dry blend. This dry blend was mixed for 15 minutes and then dry granulated in a chilsonator supplied by Fitzpatrick located in South Hackensack, N.J. to form large granules. The resulting granules were then fed into a Fitz mill having a 60 mesh screen size to form chondroitin/glucosamine granules. The chondroitin/glucosamine granules were then passed through a Sweco supplied by Sweco Inc. located in Florence, Ky. to collect particles between 20 mesh and 100 mesh particle size for tableting. Oversized particles were recycled back to the Fitz mill and undersized particles were recycled back to the chilsonator.

[0083] The chondroitin/glucosamine granules thus obtained were tableted by preparing a magnesium stearate mixture containing 3.81 parts magnesium stearate and 3.81 parts chondroitin/glucosamine granules and passing this mixture through a 30 mesh screen. The magnesium stearate mixture and the remaining chondroitin/glucosamine granules were then blended for five minutes. The resulting mixture was then tableted in accordance with the procedure described in Comparative Example 1 (target tablet weight 975.64 mg). It was found that capping was observed at a compaction pressure of 3000 lbs and tablets could not be formed.

Example 3

[0084] Tablets containing 470.59 mg of chondroitin, 526.35 mg of polyvinylpyrrolidone (PVP) granulated glucosamine, and 3.75 mg of magnesium stearate were prepared. The PVP granulated glucosamine contained 93 weight percent glucosamine and 5 wt % PVP and was obtained from Nutratech Corp., located in Fairfield, N.J. Tablets were prepared according to the procedure described for Comparative Example 1. The tablets were evaluated for disintegration time, hardness, and friability. The results are shown below in Table 2:

TABLE 2

Tablet Performance Using PVP Granulated Glucosamine	
Property	Measured Value
Disintegration time, minutes	18.5 (compressed at 7000 lbs)
Hardness, Strong-Cobb (SC)	
Compressed at 4000 pound	7.6
Compressed at 7000 pound	17.2
Compressed at 9000 pound	22.8
Friability, wt % loss	0.01% (compressed at 7000 lbs)
Weight Variation, % standard deviation	2.82% (compressed at 7000 lbs)

[0085] In a separate experiment, the PVP granulated glucosamine was compressed at various pressures with no chondroitin. The PVP granulated glucosamine did not compress into a tablet indicating that the chondroitin was acting to enhance the compactability of the PVP granulated glucosamine.

Examples 4 to 17

[0086] In Examples 4 to 17 tablets were prepared as described below where the following parameters were varied:

[0087] (a) particle size of a compaction enhancing therapeutic compound (chondroitin, particles ranging in size ranges between (i) 20 and 80 mesh, (ii) between 80 and 200 mesh, and (iii) through 200 mesh, (where the greater the mesh size, the smaller the particle size);

[0088] (b) moisture level of granulate mixture (10 wt %, 7 wt %, and less than 4 wt % moisture, based on the total weight of the granulate mixture); and

[0089] (c) amount of lubricant in tablet (0.1 wt %, 0.55 wt %, and 1.0 wt %, based on the total weight of the granulate mixture).

[0090] To an appropriately sized Hobart type blender was added 1882 parts by weight of chondroitin having one of the particle size ranges described above, 2020 parts by weight of glucosamine, and magnesium stearate, as a lubricant, at one of the levels described above to form a dry blend. This dry blend was granulated by gradually adding 500 parts by weight water at ambient temperature while mixing until granules were formed. This wet granulate mixture was then dried in an oven at 70° C. until the target moisture level (indicated in Table 2) in the granulate mixture was achieved. After drying, the granulate mixture was milled in an oscillator, supplied by Erweka, located in Heusenstamm, Germany using a 20 mesh screen.

[0091] The granulate mixtures produced were tableted on a Manesty 16 station B₃B instrument equipped with an instrumentation package, supplied by SMI Corp., capable of continuously recording compression speed, compression force, and ejection force.

Tableting speed	40 revolutions per minute (RPM)
Compression force	7000 lbs.
Tablet punches	5/16" x 3/4" caplet, B tooling
Tablet weight	1.085 gms.

[0092] The tablet compositions produced were measured for hardness, friability, disintegration time, ejection force, and weight variation according to the aforementioned test procedures.

[0093] A summary of the properties measured for each tablet composition prepared is shown below in Table 3. The values for ejection forces are based on the average of four punches, which were based on 5 revolutions.

TABLE 3

Measured Properties of Tablet Compositions Prepared								
Ex.	H ₂ O (wt %)	Lub. (wt %)	Part. Size (mesh)	Hardness (Strong-Cobb)	DT (min)	EJ Force (lbs)	Wt. Var. (%)	Friab. (%)
4	7.0	0.55	80-200	25.7	22.5	70	1.986	.06
5	7.0	1.0	20-80	15.6	25.5	57	2.106	.19
6	7.0	0.55	80-200	24	25	68	2.196	.08
7	7.0	0.1	through 200	36.5	20.5	181	1.785	.05
8	4.0	0.1	80-200	16.1	23.5	98	0.685	.1
9	10.0	0.1	80-200	41.1	21.5	123	0.81	.06
10	7.0	0.1	20-80	24.3	25	129	2.027	.08
11	7.0	0.55	80-200	23.7	23.5	66	2.252	.07
12	4.0	1.0	80-200	14.8	20.5	97	2.377	.3
13	4.0	0.55	through 200	16.5	21.5	106	2.27	.1
14	7.0	1.0	through 200	28.2	24.5	54	1.391	.07
15	10.0	0.55	through 200	35.1	23	20.4	1.626	.07
16	10.0	1.0	80-200	0	26	17.7	1.94	.14
17	10.0	0.55	20-80	24.8	20.5	26	2.165	.15

[0094] The results in Table 3 show that the method of the present invention produces tablets that are substantially free of excipients having superior properties. The results show that tablets can be formed from compaction enhancing therapeutic compounds having various particle sizes (column labeled "Part. Size"), lubricant content (column labeled "Lub."), and tablet moisture content (column labeled "H₂O"). A preferred tablet moisture is around 6.0 to 9.0 weight percent based on an analysis of the above data.

Examples 18 to 23

[0095] Tablets containing double dosage strength (label claim of 400 mg chondroitin, 500 mg glucosamine) or triple dosage strength (label claim of 600 mg chondroitin, 750 mg glucosamine) of chondroitin and glucosamine were prepared according to the following procedure. A granulate mixture was prepared by mixing for 15 minutes in a planetary blender, a dry blend of 1882.36 grams of chondroitin and 2020.20 grams of glucosamine. Following mixing, 400 grams of purified water was gradually added to the blender with mixing. Following addition of the water, the wet mixture was mixed for an additional time to produce wet granules. The wet granules were then dried in an oven at a temperature of 70° C. until a moisture level of 8.4 wt % was achieved, based on the total weight of the chondroitin/glucosamine granules. The chondroitin/glucosamine dry granules obtained were passed through an oscillator as described in the procedure for Examples 4 to 17.

[0096] Tableting mixtures were prepared, as described below, to achieve upon compaction, (a) a double strength

caplet (label claim 400 mg chondroitin and 500 mg glucosamine) containing 975.64 mg of the chondroitin/glucosamine dry granules and 3.81 mg of the magnesium stearate, and (b) a triple strength caplet (label claim 600 mg chondroitin and 750 mg glucosamine) containing 1463.46 mg of the chondroitin/glucosamine dry granules and 5.72 mg of the magnesium stearate. The tableting mixtures were prepared by mixing the desired amount of magnesium stearate (lubricant) with an approximately equal amount by weight of the dried chondroitin/glucosamine granules having a particle size of less than 30 mesh in a blender. This mixture was then passed through a 30 mesh screen. This screened mixture was added to the dried chondroitin/glucosamine granules in the blender, and mixed for an additional 5 minutes to produce the desired tableting mixture. The tableting mixture was then formed into caplets in accordance with the procedure used in Examples 4 to 17 except that the compaction pressure was varied as shown in Table 4 below. The resulting caplets were measured for hardness, disintegration time, weight variation, and friability. The results are reported below in Table 4.

TABLE 4

Properties of Caplets for Examples 4 to 23						
Ex.	Dosage Strength	Compaction Pressure (lbs)	Hardness (Strong-Cobb)	DT (min)	Wt. Var. (%)	Friab. (%)
18	Double	4000	13.7	—	—	—
19	Double	7000	25.6	19	1.05	0.09
20	Double	9000	30.4	—	—	—
21	Triple	4000	37.7	—	—	—
22	Triple	7000	>45	28.5	0.96	0.10
23	Triple	9000	>45	—	—	—

[0097] The data in Table 4 shows that the method of the present invention produces tablets that are substantially free of excipients having suitable properties such as compressibility, tablet weight variability, disintegration, and friability. Another advantage of using the present invention under the above conditions was that no capping was observed, even at compression forces up to 9000 pounds.

Examples 24 to 29

[0098] Tablet compositions were prepared according to the methods of the present invention using low amounts of a disintegrating agent. The tablets prepared contained 98.62 wt % chondroitin/glucosamine granules prepared in accordance with Examples 18 to 23, 1 wt % Croscarmellose Sodium, supplied by Blanver Farmoquímica Ltda., located in Brazil, and 0.38 wt % magnesium stearate. Also, double strength tablets containing 99.62 wt % chondroitin/glucosamine and 0.38 wt % magnesium stearate were prepared according to the procedure described in Examples 18 to 23.

[0099] The tablets containing the disintegrant were prepared by mixing in a blender for 10 minutes, the proper amounts of croscarmellose sodium and chondroitin/glucosamine granules to form a tableting mixture. The proper amount of magnesium stearate was separately mixed with an

equal amount, by weight, of the tableting mixture that had been passed through a 30 mesh screen. The magnesium stearate mixture was then passed through a 30 mesh screen. The magnesium stearate mixture was then added to the blender containing the tableting mixture and mixed for 5 minutes. This mixture was then compressed into tablets at various compaction pressures according to the procedure described in Examples 4 to 17.

[0100] The resulting tablets were then evaluated for hardness, disintegration time, friability, and weight variation.

[0101] The results are shown in Table 5 below:

TABLE 5

Properties of Tablets of Examples 24 to 29						
Ex.	Disintegrant (wt %)	Compaction Pressure (lbs)	Hardness (Strong-Cobb)	DT (min)	Wt. Var. (%)	Friab. (%)
24	0	4000	13.7	19	0.93	0.19
25	0	7000	25.6	18.5	1.09	0.091
26	0	9000	30.4	19.5	0.89	0.083
27	1	4000	14.0	17.5	0.79	0.21
28	1	7000	25.3	19	0.95	0.10
29	1	9000	30.1	18.5	0.73	0.082

[0102] The results in Table 5 show that the method of the present invention produces tablets having acceptable disintegration properties with and without the use of a disintegrant. The tablets also had acceptable hardness, friability and weight variability.

Examples 30 to 32

[0103] To a planetary blender was added 106.33 grams of chondroitin and 2020 grams of glucosamine. This mixture was mixed for 15 minutes in the blender to form a dry blend. This dry blend was granulated by gradually adding 200 grams of purified water at ambient temperature while mixing until granules were formed. This wet granulate mixture was then dried in an oven at 700° C. until a moisture level 1.50 wt % in the granulate mixture was achieved. After drying, the granulate mixture was passed through an oscillator according to Examples 4 to 17. To produce granules containing 5 wt % chondroitin and 95 wt % glucosamine.

[0104] Tablets were prepared by mixing in a blender for 15 minutes, 2126.53 grams of the chondroitin/glucosamine granules (containing 5 wt % chondroitin), and 1776.03 grams of chondroitin to form a tableting mixture. The proper amount of magnesium stearate was separately mixed with an equal amount, by weight, of the tableting mixture that had been passed through a 30 mesh screen. The magnesium stearate mixture was then passed through a 30 mesh screen. The magnesium stearate mixture was then added to the blender containing the tableting mixture and mixed for 5 minutes. This mixture was then compressed into tablets at various compaction pressures according to the procedure described in Examples 4 to 17.

[0105] The resulting tablets were then evaluated for hardness, disintegration time, and weight variation. A summary of the properties measured for each tablet prepared is shown below in Table 6

TABLE 6

Properties of Tablets Formed from 5 wt % Chondroitin Granules				
Ex.	Compaction Pressure (lbs)	Hardness (Strong-Cobb)	DT (min)	Wt. Var. (%)
30	4000	13.7	18.5	1.09
31	7000	23.5	19	0.71
32	9000	33.6	19.5	0.71

[0106] The data in Table 6 shows that suitable tablets can be formed from granules containing 5 wt % of chondroitin and 95 wt % glucosamine, ungranulated chondroitin, and magnesium stearate. Based on the results of Example 3, using 5 wt % PVP/glucosamine granules, chondroitin appears to be a more effective compacting agent for glucosamine. This is a surprising result considering that PVP is commonly used as a binder for chondroitin and glucosamine tablets.

Examples 33 to 44

[0107] Tablets containing 500 mg glucosamine, 400 mg chondroitin, 20 mg Vitamin C, 133 IU Vitamin D and 167 mg calcium were prepared by using (a) ungranulated glucosamine and chondroitin, (b) glucosamine granulated with 5 wt % chondroitin, and (c) fully granulated glucosamine and chondroitin. Three different tablet compositions were prepared as shown in Table 7 below:

TABLE 7

Tablet Compositions for Examples 33 to 44			
Ingredients	A	B	C
	(Ungranulated, mg)	(5 wt % Granulated, mg)	(Fully Granulated, mg)
Chondroitin, 85%	470.59	444.01	0.0
Glucosamine, 99 wt %	505.05	0.0	0.0
5 wt % granulated chondroitin/glucosamine	0.0	531.63	0.0
fully granulated chondroitin/glucosamine	0.0	0.0	975.64
Vitamin C-90	25.82	25.82	25.82
Vitamin D	1.84	1.84	1.84
Calcium Carbonate DC	473.13	473.13	473.13
Magnesium Stearate	7.50	7.50	7.50
Total	1483.93	1483.93	1483.93

[0108] The chondroitin/glucosamine granules containing 5 weight percent chondroitin, were prepared according to the procedure used in Examples 30 to 32, except that the wet granules were dried to a LOD content of 1.5 weight percent. The fully granulated chondroitin/glucosamine granules were prepared according to the procedure used in Examples 18 to 23, except that the wet granules were dried to a LOD content of 6.5 weight percent.

[0109] Tablets were prepared by mixing Vitamins C-90 and D in a blender for 10 minutes to form a vitamin mixture. Also, magnesium stearate and an equal amount, by weight, of the calcium carbonate were mixed separately and passed through a 30-mesh screen. To an appropriately sized blender

was added the vitamin mixture, the remaining calcium carbonate, and the glucosamine and chondroitin (granulated or ungranulated as specified in Table 7 above). This mixture was blended for 10 minutes after which the magnesium stearate mixture was added and blended for 5 more minutes. The resulting tableting mixtures were tabletted according to the procedure in Examples 4 to 17 at various pressures. The results are shown below in Table 8.

TABLE 8

Performance of Tablet Compositions A through C						
Ex.	Tablet Composition	Compaction Pressure (lbs)	Hardness (Strong-Cobb)	DT (min)	WL Var. (%)	Friab. (%)
33	A	4000	10.2	15	2.61	6.34
34	A	6000	17.1	19	2.14	1.10
35	A	8000	26.7	21	1.78	capped
36	A	9000	27.2	21.5	2.32	capped
37	B	4000	19.0	18.5	0.90	0.23
38	B	6000	30.8	21.5	0.56	0.06
39	B	8000	40.2	24	0.61	0.02
40	B	9000	>45	24.5	0.92	0.01
41	C	4000	20.7	23	1.05	0.22
42	C	6000	33.5	27.5	0.76	0.08
43	C	8000	42.2	29.5	0.66	0.07
44	C	9000	>45	29	0.69	0.06

[0110] For compositions containing the ungranulated glucosamine and chondroitin (i.e., composition A), the tablets could be compressed up to 6000 pounds without capping. For compositions containing glucosamine granulated with chondroitin (i.e., compositions B and C), the addition of other therapeutic compounds in the tablet did not hinder the performance properties of the tablet.

Example 45 to 48

[0111] Tablets containing Vitamin C (i.e., ascorbic acid) and chondroitin were prepared using Vitamin C as is (ungranulated) and Vitamin C granulated with 5 wt % chondroitin (as a compaction enhancing therapeutic compound). Two different tablet compositions were prepared as shown in Table 9 below:

TABLE 9

Tablet Compositions for Examples 45 to 48 (500 mg Vitamin C label claim)		
Ingredients	D (Ungranulated, mg)	E (5 wt % Granulated, mg)
Chondroitin, 85%	27.63	0.0
Ascorbic acid fine powder	525	0.0
5 wt % granulated chondroitin/ascorbic acid	0.0	552.63
Microcrystalline cellulose	22.76	22.76
Stearic acid	5.74	5.74
Magnesium stearate	7.50	7.50
Total	582.02	582.02

[0112] The chondroitin/ascorbic acid granules were prepared by mixing in a blender for 10 minutes, the appropriate amounts of chondroitin and ascorbic acid to form granules

containing 5 wt % chondroitin and 95 wt % ascorbic acid. Following mixing, water was gradually added with mixing until uniform granules were formed and the mixture was free of loose powder. The granules produced were dried at 75° C. until the moisture content of the granules was less than 0.2 wt %. The dried granules were passed through an oscillator equipped with a 20 mesh screen according to the procedure in Examples 4 to 17.

[0113] To form the tableting mixtures, ascorbic acid (granulated or ungranulated) and chondroitin (if ungranulated) were mixed in a blender for 10 minutes. A mixture of stearic acid, magnesium stearate, and an equal amount by weight of microcrystalline cellulose (based on the combined weight of the stearic acid and magnesium stearate) was mixed separately in a blender for 2 minutes and passed through a 20 mesh screen. The magnesium stearate mixture was then added to the blender containing the ascorbic acid and chondroitin, and mixed for an additional 5 minutes. The tableting mixtures were then compressed according to the procedure described in Examples 4 to 17 at various pressures. The results are shown below in Table 10.

TABLE 10

Tablet Performance for Examples 45 to 48						
Ex.	Tablet Composition	Compaction Pressure (lbs)	Hardness (Strong-Cobb)	DT Time (min)	WL Var. (%)	Friab. (%)
45	D	2000	—	—	—	capping
46	E	4000	8.6	5.5	0.68	0.66
47	E	5000	8.9	6	0.66	capped
48	E	6000	8.0	6.5	0.32	capped

[0114] The results in Table 10 show that when chondroitin is granulated with ascorbic acid, the compactability of the ascorbic acid can be significantly improved in comparison to simply admixing the ascorbic acid with the chondroitin.

Examples 49 to 50

[0115] Grape seed extract was evaluated for its ability to act as a compaction enhancing therapeutic compound for L-arginine HCl. The following procedure was used for preparing granules of grape seed extract and L-arginine.

[0116] To a Hobart blender was added 900 grams of L-Arginine HCl. A granulating fluid was prepared by dispersing 100 grams of grape seed extract (90 wt % polyphenols) in 150 grams of isopropanol. To the isopropanol/grape seed extract mixture was added with stirring 100 grams of water in three equal additions (i.e., about 33.3 grams each). The granulating fluid was then added to the L-arginine with mixing to form granules. The granules were then dried in an oven at 50° C. until the moisture in the granules was 1.2 wt %. The dried granules were then passed through an oscillator according to the procedure used in Examples 4 to 17.

[0117] Tableting mixtures were prepared using (a) ungranulated grape seed extract and arginine and (b) granulated grape seed extract and arginine prepared as described above. The compositions of the tableting mixtures (in weight per tablet) are shown in Table 11.

TABLE 11

Tablet Compositions Containing Grape Seed Extract and L-Arginine HCl		
Ingredients	F (Ungranulated, mg)	G (Granulated, mg)
Grape Seed/Arginine granules	0.0	267
L-Arginine HCl	240	0.0
Grape seed extract (90 wt % polyphenols)	27	0.0
Magnesium stearate	3.0	3.0
Total	270	270

[0118] To form the tableting mixtures, the magnesium stearate was separately mixed with an equal amount by weight of either the grape seed extract/arginine granules (composition G) or a blend of the grape seed extract and L-arginine (composition F) that had been passed through a 30 mesh screen. To this magnesium stearate mixture was added the remaining amount of the grape seed extract and arginine HCl in the appropriate granulated or ungranulated form. These ingredients were then mixed for 2 minutes. The tableting mixtures were then compressed according to the procedure described in Examples 4 to 17 at various pressures, except that $\frac{3}{8}$ " SC punches were used. The results are shown below in Table 12.

TABLE 12

Tablet Performance of Tablets Containing Grape Seed Extract and L-Arginine HCl				
Ex.	Tablet Composition	Hardness (Strong-Cobb)	DIT Time (min)	Friab. (%)
49	F	—	—	—
50	G	7.2	4	0.90

[0119] The results in Table 12 show that when grape seed extract is granulated with L-arginine a tableting mixture is formed that can be tableted. The ungranulated grape seed extract and L-Arginine could not be formed into a tablet under the same conditions used to form a tablet from the grape seed extract/arginine granules.

[0120] There have thus been described certain preferred embodiments of the present invention. While preferred embodiments have been disclosed and described, it will be recognized by those with skill in the art that variations and modifications are within the true spirit and scope of the invention. The appended claims are intended to cover all such variations and modifications.

What is claimed is:

1. A tablet composition comprising, on a dry-weight basis:

- from about 3 weight percent to about 99.5 weight percent of a compaction enhancing therapeutic compound;
- from about 0.5 weight percent to about 97 weight percent of at least one second therapeutic compound that is different from the compaction enhancing therapeutic compound, wherein the compaction enhancing therapeutic compound enhances the compaction of the second therapeutic compound; and

(c) less than about 15 weight percent non-aesthetic excipients.

2. The tablet composition of claim 1 wherein the compaction enhancing therapeutic compound is in intimate admixture with the second therapeutic compound.

3. The tablet composition of claim 1 wherein the tablet composition has a friability of less than about 1 weight percent, and an increased hardness of at least about 10% relative to a tablet of the same weight, shape, and size, compressed under the same conditions, and not containing the compaction enhancing therapeutic compound.

4. The tablet composition of claim 1 wherein the compaction enhancing therapeutic compound is selected from the group consisting of glycosaminoglycans; herbal based extracts; botanical based extracts; vitamins; salt forms of minerals; anti-inflammatory agents; antibiotics; cholesterol lowering agents; and combinations thereof.

5. The tablet composition of claim 4 wherein the glycosaminoglycan is heparin, dermatan sulfate, chondroitin, sulodexide or a pharmaceutically acceptable salt thereof; the herbal or botanical based extract is St. John's Wort extract, horse chestnut, ginseng, ginkgo biloba, grape seed extract or a pharmaceutically acceptable salt thereof; the vitamin is niacinamide ascorbate or a pharmaceutically acceptable salt thereof; the anti-inflammatory agents is naproxen or a pharmaceutically acceptable salt thereof; the antibiotic is cephalosporin or a pharmaceutically acceptable salt thereof; the cholesterol lowering agent is cholestyramine or a pharmaceutically acceptable salt thereof.

6. The tablet composition of claim 5 wherein the compaction enhancing therapeutic compound comprises a glycosaminoglycan, grape seed extract, or combinations thereof.

7. The tablet composition of claim 1 wherein the second therapeutic compound is a non-compaction enhancing therapeutic compound.

8. The tablet composition of claim 7 wherein the compaction enhancing therapeutic compound comprises a glycosaminoglycan and the second therapeutic compound comprises an aminosugar.

9. The tablet composition of claim 8 wherein the glycosaminoglycan is heparin, dermatan sulfate, chondroitin, sulodexide, or a pharmaceutically acceptable salt thereof, and the aminosugar is glucosamine, or a pharmaceutically acceptable salt thereof.

10. The tablet composition of claim 9 wherein the glycosaminoglycan is chondroitin or a pharmaceutically acceptable salt thereof and the glucosamine is N-acetyl glucosamine sulfate, glucosamine hydrochloride, or glucosamine sulfate.

11. The tablet composition of claim 8 wherein the tablet composition comprises from about 3 weight percent to about 99.5 weight percent glycosaminoglycan; and from about 0.5 weight percent to about 97 weight percent aminosugar.

12. The tablet composition of claim 8 wherein the tablet composition further comprises at least a third therapeutic compound selected from the group consisting of kelp, manganese ascorbate, sodium ascorbate, calcium ascorbate, Vitamin C, dried powder forms of Vitamin A, Vitamin D, Vitamin E, Vitamin K, and beta carotene; Vitamin B₆, niacin, phosphorous containing salts, zinc containing salts, copper containing salts, calcium containing salts, calcium citrate, calcium carbonate, oyster shell, magnesium, manganese sulfate, boron, estrogen, and combinations thereof.

13. The tablet composition of claim 8 wherein the amount of the non-aesthetic excipient is less than about 5 weight percent.

14. The tablet composition of claim 13, wherein the non-aesthetic excipient comprises a lubricant.

15. A tablet composition comprising, on a dry weight basis:

- (a) from about 5 weight percent to about 50 weight percent of a compaction enhancing therapeutic compound that is a glycosaminoglycan;

- (b) from about 10 weight percent to about 95 weight percent of at least one second therapeutic compound that is an aminosugar, wherein the compaction enhancing therapeutic compound enhances the compaction of the second therapeutic compound and is in intimate admixture with the second therapeutic compound; and

- (c) less than about 10 weight percent non-aesthetic excipients.

* * * * *



PODER ESPECIAL

Yo, **WALTER TANAKA TATEKAWA**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **PROCAPS S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 14 167105, titulada "COMPRIMIDO ANTIÁCIDO", cuyo titular es **GLAXOSMITHKLINE LLC.** publicada en la gaceta No. 702 del 11 de Agosto de 2014.

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

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

Dado y Firmado en Barranquilla (Colombia) a los 27 días del mes de Octubre de 2014.

PROCAPS S.A.

C.C. N° 16'251.923

NIT: 890.106.527-5

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51.975.664

T.P. 83823 del C.S.J

Barranquilla, 29 de Octubre de 2014

Hr:11:51:35



***** Pag. 1
 CAMARA DE COMERCIO
 DE BARRANQUILLA
 13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

"EL PRIMER JUEVES HÁBIL DE DICIEMBRE DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA DE LA CÁMARA DE COMERCIO DE BARRANQUILLA POR AFILIADOS. LA INSCRIPCIÓN DE LISTAS DE CANDIDATOS DEBE HACERSE DURANTE LA SEGUNDA QUINCENA DEL MES DE OCTUBRE. PARA INFORMACIÓN DETALLADA PODRÁ COMUNICARSE AL TELÉFONO 3303756, O DIRIGIRSE A LA SEDE ADUANA DE ESTA ENTIDAD, O A TRAVÉS DE LA PÁGINA WEB www.camarabaq.org.co."

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

C E R T I F I C A

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

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

"PRODUCTORA DE CAPSULAS DE GELATINA S.A. "PROCAPS S.A."-----

C E R T I F I C A

Que por Escritura Pública No. 3,615 del 06 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Dic/bre de 1996 bajo el No. 67,218 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion LABORATORIOS PROCAPS S.A

C E R T I F I C A

Que por Escritura Pública No. 3,775 del 18 de Dic/bre de 1996, otorgada en la Notaria 2a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 23 de Enero de 1997 bajo el No. 67,704 del libro respectivo, la sociedad antes mencionada-----
cambio de razon social, por la denominacion PROCAPS S.A. -----

C E R T I F I C A

Que por Escritura Pública No. 16 del 08 de Enero de 2013, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 06 de Febrero de 2013 bajo el No. 251,483 del libro respectivo, la sociedad antes mencionada-----
se transformo en por acciones simplificada bajo la denominación de PROCAPS S.A.S-----

C E R T I F I C A

Que por Escritura Pública No. 1,890 del 23 de Julio de 2013, otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 20 de Agosto de 2013 bajo el No. 258,524 del libro respectivo, la sociedad antes mencionada-----
se transformo en sociedad anonima bajo la denominación de -----
PROCAPS S.A.-----

C E R T I F I C A

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero	aaaa/mm/dd	Notaria	No. Insc o Reg	aaaa/mm/dd
39	1979/01/18	Notaria 3a. de Barranquilla.	9,452	1979/01/24
992	1981/04/30	Notaria 1a. de Barranquilla.	13,112	1981/05/06
1,464	1982/08/27	Notaria Unica de Soledad	15,533	1982/09/08
2,744	1983/08/18	Notaria Unica de Soledad	17,416	1983/08/26
3,826	1984/07/16	Notaria Unica de Soledad	19,554	1984/07/27
3,835	1985/08/26	Notaria Unica de Soledad	22,230	1985/09/04
2,260	1986/09/10	Notaria Unica de Soledad.	24,995	1986/09/15
1,849	1989/07/11	Notaria 2a. de Barranquilla.	33,909	1989/07/13
444	1990/02/21	Notaria 2a. de Barranquilla.	36,101	1990/03/16
3,090	1991/12/17	Notaria 2a. de Barranquilla	43,993	1992/01/28
269	1993/02/01	Notaria 2a. de Barranquilla	48,428	1993/02/16

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

Barranquilla, 29 de Octubre de 2014

Hr:11:51:35



***** Pag. 2

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

2,342	1993/07/28	Notaria 2a. de Barranquilla	50,582	1993/08/10
3,652	1993/11/09	Notaria 2a. de Barranquilla	51,798	1993/11/22
3,615	1996/12/06	Notaria 2a. de Barranquilla	67,218	1996/12/20
89	1997/01/16	Notaria 2a. de Barranquilla	67,704	1997/01/23
2,070	1997/07/17	Notaria 2a. de Barranquilla	70,627	1997/07/31
2,281	1997/08/04	Notaria 2a. de Barranquilla	70,813	1997/08/14
765	1999/04/22	Notaria 3a. de Barranquilla	80,628	1999/04/23
459	2001/02/21	Notaria 2a. de Barranquilla	91,502	2001/02/23
2,608	2001/10/05	Notaria 2a. de Barranquilla	95,771	2001/11/08
1,730	2004/07/29	Notaria 2. de Barranquilla	112,999	2004/08/26
416	2005/03/03	Notaria 2. de Barranquilla	116,364	2005/03/10
1,613	2005/07/28	Notaria 2. de Barranquilla	119,322	2005/08/18
710	2009/05/05	Notaria 3 a. de Barranquilla	150,130	2009/06/30
1,054	2009/06/25	Notaria 3 a. de Barranquilla	150,130	2009/06/30
16	2013/01/08	Notaria 3a. de Barranquilla	251,483	2013/02/06
16	2013/01/08	Notaria 3a. de Barranquilla	251,483	2013/02/06
2,060	2013/08/02	Notaria 3 a. de Barranquilla	258,507	2013/08/16
1,890	2013/07/23	Notaria 3a. de Barranquilla	258,524	2013/08/20

C E R T I F I C A

Que de acuerdo con la(s) escritura(s) o el(los) documento(s) arriba citado(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

PROCAPS S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

C E R T I F I C A

Direccion Comercial:

CL 80 No 78 B - 201 en Barranquilla.

Email

Comercial:

jcelis@procaps.com.co

Telefono: 3719278.

Direccion Judicial:

CL 80 No 78 B - 201 en Barranquilla.

Email

Notificacion

Judicial:

jcelis@procaps.com.co

Telefono: 3719278.

C E R T I F I C A

Que su total de activos es: \$ 667,990,131,000=.

SEISCIENTOS SESENTA Y SIETE MIL NOVECIENTOS NOVENTA MILLONES CIENTO TREINTA Y UN MIL PESOS COLOMBIANOS.

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

C E R T I F I C A

DURACION: Que la sociedad no se halla disuelta y su término de duración se fijó hasta el 31 de Dic/bre de 2100.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad será: a) La fabricación, importación y comercialización de alimentos procesados y suplementos dietarios. b) La fabricación de cápsulas y otros productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias químicas, farmacéuticas, alimenticias y cosméticas, para uso y consumo humano y veterinario. c) La investigación, desarrollo y fabricación de toda clase de productos y sustancias químicas, farmacéuticas, alimenticias y cosméticas para uso y consumo humano, animal y vegetal. d) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricación de sustancias químicas, farmacéuticas, alimenticias y cosméticas, así como la comercialización interna y externa de los productos terminados. e) La compra, venta, importación, exportación y distribución de toda clase de elementos instrumentales y equipos médicos, quirúrgicos, odontológicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportación, fabricación, importación, distribución de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agentes de personas naturales y jurídicas, nacionales y extranjeras en la realización de operaciones o transacciones relacionadas con la industria farmacéutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los servicios de asesorías y consultoría en las áreas administrativas, de mercadeo, análisis clínico, asistencia técnica, investigación, costos y producción, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., así como los de publicidad y promoción de productos químicos, alimenticios, cosméticos y farmacéuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier título, empresa o establecimientos dedicados a la investigación, desarrollo, fabricación o comercialización de productos químicos, farmacéuticos, alimenticios, hospitalarios o cosméticos. En desarrollo de su objeto principal, la sociedad podrá tomar interés social como accionista, socio o fundador de empresas que tengan igual o similar objeto, comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en préstamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar

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



***** Pag. 3

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el país y en el exterior y, en general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o la de sus socios. La sociedad podrá garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podrá inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.-----

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acción
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,302,700,000	*****1,302,700	*****1,000
Pagado		
\$*****1,302,700,000	*****1,302,700	*****1,000

C E R T I F I C A

ADMINISTRACION: Corresponde a la Junta Directiva las siguientes funciones entre otras: Autorizar cualquier acto o contrato cuya cuantía sea superior al equivalente en pesos colombianos a UN MILLON DE DÓLARES de los Estados Unidos de América(US\$ 1.000.000.00), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerirá que la operación sea aprobada con el voto de por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendrá un Presidente, que ejercerá la representación legal de la sociedad y tendrá las siguientes atribuciones entre otras: Ejercer la Representación legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y los presentes estatutos; Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en, pesos colombianos a UN MILLON DE DÓLARES de los Estados Unidos de América(US\$1.000.000.00)liquidados

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

a la tasa de cambio representativa del mercado vigente el día en que surta la a-probación o celebración del acto. El Vicepresidente tendrá las siguientes facultades entre otras: Ejercer la Representación Legal de la Sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social de conformidad con lo previsto en las leyes y en los presentes estatutos.

Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en, pesos colombianos a QUINIENTOS MIL DÓLARES de los Estados Unidos de América(US\$500.000), liquidados a la tasa de cambio representativa del mercado vigente el día en que surta la a-probación o celebración del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble acciones, cuotas o partes de interés, inversiones y, todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente. El Gerente General tendrá las siguientes facultades entre otras: Ejercer la Representación legal de la Sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y los presentes estatutos. Constituir apoderados judiciales y extrajudiciales, recibir notificaciones, absolver interrogatorios de parte, confesar obligaciones de la sociedad, transigir, desistir y allanar a la sociedad en cualquier asunto judicial; Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantía sea igual o inferior al equivalente en pesos colombianos a CIEN MIL DÓLARES de los Estados Unidos de América(US\$100.000)), liquidados a la tasa de cambio representativa del mercado vigente el día en que se surta la aprobación o celebración del acto, siempre que no se trate de enajenar a cualquier título bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interés, inversiones y todo tipo de derechos de la sociedad, o de constituir gravámenes sobre cualquiera de los anteriores, facultades que radican exclusiva y privativamente en cabeza del Presidente.

C E R T I F I C A

Que por Escritura Pública No. 1,890 del 23 de Julio de 2013, otorgada en la Notaria 3a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Agosto de 2013 bajo el No. 258,525 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben
2. Minski Gontovnik Meyer

CC.*****7,463,982
CC.*****7,461,324

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



***** Pag. 4

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

3. Minski Gontovnik Jose

CC.*****8,671,834

C E R T I F I C A

Que según Acta No. 116 del 27 de Junio de 1997 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 15 de Agosto de 1997 bajo el No. 70,838 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Presidente.

Minski Gontovnik Ruben

CC.*****7463982

C E R T I F I C A

Que según Acta No. 406 del 02 de Sep/bre de 2004 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Sep/bre de 2004 bajo el No. 113,263 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Suplente del Gerente.

Tanaka Tatekawa Walter

CC.*****16251923

C E R T I F I C A

Que según Acta No. 658 del 07 de Dic/bre de 2011 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 09 de Dic/bre de 2011 bajo el No. 176,066 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Vicepresidente

Minski Gontovnik Jose

CC.*****8671834

Suplente del Presidente

Minski Gontovnik Meyer

CC.*****7461324

Suplente del vicepresidente

Carvajalino Pagano Marcela

CC.*****22579748

C E R T I F I C A

Que según Acta No. 725 del 08 de Agosto de 2014 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 01 de Sep/bre de 2014 bajo el No. 272,947 del libro respectivo,

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Gerente General Hidalgo Suarez Francisco	CC.*****19222967

C E R T I F I C A

Que según Acta No. 159 del 16 de Enero de 2012 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: PROCAPS S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 23 de Enero de 2012 bajo el No. 237,199 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre	Identificación
Revisor Fiscal Principal Rodriguez Rey Jose Luis	CC.*****72,001,912

C E R T I F I C A

Que por Escritura Pública No. 2,784 del 07 de Dic/bre de 2007, otorgada en la Notaria 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 20 de Dic/bre de 2007 bajo el No. 3,492 del libro respectivo,-----
y las inscripciones 3.492-1, 3.493, 3.494, 3.495, 3.496, 3.497, ----
3.498, 3.499, 3.500, 3.501, 3.502, 3.503, 3.504, 3.505, 3.506, ----
3.507, Consta que RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, -----
obrando como Presidente y Representante Legal de la sociedad C.I. NATURMEGA S.A., que obrando en su condicion de Presidente y -----
Representante Legaql de la sociedad PROCAPS S.A., el presidente ----
debidamente facultado por los Estatutos Sociales y por el Maximo Organ Social, otorga los siguientes poderes: Otorgar poder -----
general, amplio y suficiente a los doctores JOSEFINA DEL CARMEN ----
MIELES BUELVAS CC.No.33.138.497; a MARCELA CARVAJALINO PAGANO -----
CC.No.22.579.748; CRISTINA VIOLI FRANCESCHINI CC.No.22.463.716, con las facultades que se transcriben a continuacion: a.- Para que ----
representen a la sociedad PROCAPS S.A, ante todo tipo de -----
autoridades administrativas y jurisdiccionales, en asuntos de -----
naturaleza civil, laboral, comercial, penal, aduanera, cambiaria, tributaria, policiva, administrativa y fiscal. b.- Contestar y ----
presentar demandas, requerimientos, recursos, pedir y aportar -----
pruebas, recibir, notificarse, ejercer la accion de tutela, -----
tramitar incidente de desacato, comparecer en los procesos que ----
cursen contra la sociedad, allanarse en nombre de la sociedad en los asuntos que sean necesarios, transigir, desistir, sustituir, renunciar y reasumir el poder. c.- La facultad expresa de -----
conciliar, por tanto pueden llegar a acuerdos conciliatorios, -----
transaccionales, judiciales o extrajudiciales o extrajudiciales, cualquiera que sea su cuantia, para lo cual las apoderadas deben aportar la autorizacion simple y escrita del Representante legal de la sociedad. d.- Podran presentar solicitudes de devolucion y/o compensacion de impuestos, ventas y rentas, recibir los pagos por las devoluciones y adelantar todo tramite o proceso administrativo ante la DIAN, de tal forma que en ningun momento quede sin -----
representacion legal de la sociedad. PODERES ESPECIALES: a.- Se ----

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



***** Pag. 5

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

confiere poder especial amplio y suficiente a las personas que se determinan seguidamente, que conforman el grupo A y B, para, para que conjuntamente suscriban contratos de suministros de mercancías y servicios con entidades oficiales, hasta la suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE AMERICA (US800.000.00), ----- liquidados a la tasa representativa del mercado vigente en el día que se realice la respectiva transacción. Grupo A. WALTER NANAKA TATEKAWA CC.No.16.251.923, CLAUDIA TANGARIFE CASTILLO ----- CC.No.41.660.293, CARMEN ALICIA FLOREZ CC.No.22.434.044, IVAN ----- VILLAREAL CAMACHO CC.No.91.201.749, CARMEN ALICIA HERRERA ----- DIAZGRANADOS CC.No.22.377.540, DAVID ANTONIO CHARRIS GIRALDO ----- CC.No.19.341.274, RICARDO DORADO HURTADO CC.No.79.715.772, JAIME FORERO LLINAS CC.No.19.300.593. b.- Se confiere poder especial ----- amplio y suficiente al señor WILLIAM ALBERTO BARROS CERRA ----- CC.No.8.715.941, para que en nombre y representación de PROCAPS ---- S.A., suscriban declaraciones cambiarias, aduaneras y tributarias a que este obligada la sociedad, en el giro normal de sus negocios y operaciones sociales, por tanto quedan facultados para firmarlas, como también los demás documentos relacionados con ellas, ----- notificarse, aportar y solicitar las pruebas que sean necesarias. c.-Otorgar poder especial amplio y suficiente al señor MARLON ----- TATIS PAREDES CC.No.72.176.874 y al señor WILLIAM ALBERTO BARROS CERRA CC.No.8.715.941, para que en nombre y representación de ----- PROCAPS S.A., suscriban las declaraciones, reportes y cualquier documento relacionado con los trámites o registros de Comercio ----- Exterior y o cualquier entidad del Estado que haga sus veces: d) Otorgar poder especial amplio y suficiente a la doctora CARMEN ----- ALICIA HERRERA DIAZGRANADOS, CC.No.22.377.540 y al doctor WALTER TANAKA TATEKAWA, CC.No.16.251.923, para que en nombre y ----- representación de PROCAPS S.A.; endosen los títulos valores de la sociedad hasta por la suma de UN MIL MILLONES DE PESOS ----- (1.000.000.000.00) M.L. CUARTO: El representante legal de la ----- sociedad PROCAPS S.A.; doctor RUBEN MINSKI GONTOVNIK, manifiesta que la presente reforma fue aprobada por la Asamblea General ----- Extraordinaria de Accionista de PROCAPS S.A., con observancia de las disposiciones legales y estatutarias.-----

C E R T I F I C A

Que por Escritura Pública No. 1,933 del 16 de Sep/bre de 2008, otorgada en la Notaría 2 a. de Barranquilla cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Octubre de 2008 bajo el No. 3,748 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, que comparece en su condición de Presidente y Representante Legal de la

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

Sociedad PROCAPS S.A., confiere por medio de este instrumento -----
publico Poder especial Amplio y Suficiente a la doctora MILENA -----
ESCAFFI PARDO, C.C. No. 32.758.420, para que en nombre y -----
representacion de PROCAPS S.A., suscriba declaraciones cambiarias,
aduaneras y tributarias a que este obligada la sociedad en el giro
normal de sus negocios y operaciones sociales, por tanto queda ----
facultada para firmar, como tambien los demas documentos -----
relacionados con ellas, notificarse, aportar y solicitar las -----
pruebas que sean necesarias.-----

C E R T I F I C A

Que por Documento Privado del 09 de Abril de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 20 de Abril de
2010 bajo el Nro 4,201 del libro respectivo,-----
Consta que el señor RUBEN MINSKI GONTOVNIK, C.C. No. 7.463.982, ----
quien obra en el caracter de Presidente y/o Representante legal de
la sociedad PROCAPS S.A., que por medio de este instrumento -----
publico, otorga Poder Especial Amplio y Suficiente a la Doctora ----
MONICA DE HART DE OCHOA, identificada con C.C. No. 32.676.025, para
que en nombre y representacion de la sociedad, Endose las Facturas
Nacionales e Internacionales hasta por la suma de UN MIL MILLONES DE
PESOS (\$1.000.000.000.00)M.L. La doctora Monica de Hart de Ochoa,
queda facultada para realizar todo acto o tramite necesario para el
cabal cumplimiento del presente mandato.-----

C E R T I F I C A

Que por Documento Privado del 10 de Junio de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 13 de Julio de
2010 bajo el Nro 4,228 del libro respectivo,-----
consta que el señor RUBEN MISNKI GONTOVNIK, cc. No. 7.463.982 en su
condicion de Presidente y representante legal de PROCAPS S.A., ----
confiere poder especial, amplio y suficiente al señor RICARDO DORADO
HURTADO cc. No. 79.715.772 para que represente a la sociedad, ante
el INVIMA, Fondo Nnacional de estupefacientes e ICA, con el fin que
gestione, tramite o presente las diferentes solicitudes y -----
peticiones de la empresa, segun la competencia de estas entidades.
Por lo anterior, el Señor RICARDO DORADO HURTADO, queda facultado
para presentar, gestionar, tramitar y firmar las diferentes -----
solicitudes y peticiones de la empresa, segun la competencia de ----
estas entidades, como tambien presentar y firmar todo los -----
documentos relacionados con estas solicitudes, notificarse de -----
cualquier acto administrativo que expidan, aportar y solicitar las
pruebas que sean necesarias, desistir, y en general a realizar todo
tramite o acto necesario de tal forma que la sociedad en ningun ----
momento quede sin representacion legal ante estas entidades, en ----
cumplimiento fiel al mandato otorgado.-----

C E R T I F I C A

Que por Documento Privado del 03 de Agosto de 2010, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 24 de Agosto

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



***** Pag. 6

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

de 2010 bajo el Nro 4,258 del libro respectivo,-----
 consta que RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta
 vecindad, identificado con la cédula de ciudadanía No.7.463.982,
 expedida en Barranquilla, en mi condición de Representante legal
 y/o Presidente de la sociedad PROCAPS S. A., conforme a las -----
 facultades otorgadas por los Estatutos Sociales, todo lo cual -----
 demuestro con el certificado de existencia y representación legal
 expedido por la Cámara de Comercio de Barranquilla, que adjunto a
 este escrito, me permito manifestarles que confiero poder especial,
 amplio y suficiente al señor MARIO LÓPEZ LEON, varón, mayor de -----
 edad, de esta vecindad, identificado con la cédula de ciudadanía
 No.72.311.558, expedida en Puerto Colombia (Atlántico), para que en
 nombre y representación de la sociedad, realice los siguientes -----
 actos: 1. Endosar las Facturas Nacionales e Internacionales de esas
 compañías hasta por la suma de UN MIL MILLONES DE PESOS -----
 (\$1.000.000.000.00) Moneda Legal. 2. Suscribir Declaraciones -----
 Cambiarias, Aduaneras y Tributarias a las que esta obligada la -----
 sociedad en el giro ordinario de sus negocios, quedando facultado
 para notificarse, aportar y solicitar pruebas relacionados con las
 declaraciones Cambiarias. El señor MARIO LÓPEZ LEÓN, queda -----
 facultado para notificarse, aportar y solicitar pruebas, presentar
 escritos en caso que resulte necesario en general a realizar todo
 acto, diligencia o tramite que considere indispensable para el -----
 cabal cumplimiento del presente mandato.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en
 Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de
 2012 bajo el Nro 4,813 del libro respectivo,-----
 consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
 C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
 Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las
 facultades otorgadas por los Estatutos Sociales, me permito -----
 manifestarles que confiero poder especial, amplio y suficiente a
 MONICA DE HART DE OCHOA, identificada con C.C.32.676.025, para que
 en nombre y representación de la sociedad, realice operaciones de
 carácter Financiero con la firma conjunta de un(1)miembro del Grupo
 A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin -----
 perjuicios de las facultades otorgadas anteriormente a algunos de
 los funcionarios e inscritas en la Cámara de Comercio de esta -----
 ciudad, como determino: -----
 GRUPO A -----

1. Monica De Hart De Ochoa -----

C.c. No. 32.676.025 -----

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A. -----
NIT: 890.106.527-5. -----

2. Javier Otero Arteaga -----
C.C. No. 91.263.993 -----
3. Gethel Moreno Romero -----
C.C. No.32.689.958 -----
GRUPO B -----
Marcela carvajalino Pagano -----
C.C. 22.579.748 -----
Walter Tanaka Tatekawa -----
C.C. 16.251.923 -----
Alain Cortesi Brunner -----
Cedula Extranjeria 215404 -----
a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,814 del libro respectivo, -----
consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las facultades otorgadas por los Estatutos Sociales, me permito -----
manifestarles que confiero poder especial, amplio y suficiente a JAVIER OTERO ARTEAGA, identificado con C.C.91.263.993, para que ----
en nombre y representación de la sociedad, realice operaciones de carácter Financiero con la firma conjunta de un(1)miembro del Grupo A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin -----
perjuicios de las facultades otorgadas anteriormente a algunos de los funcionarios e inscritas en la Cámara de Comercio de esta -----
ciudad, como determino: -----

GRUPO A -----
1. Monica De Hart De Ochoa -----
C.c. No. 32.676.025 -----
2. Javier Otero Arteaga -----
C.C. No. 91.263.993 -----
3. Gethel Moreno Romero -----
C.C. No.32.689.958 -----
GRUPO B -----
Marcela carvajalino Pagano -----
C.C. 22.579.748 -----
Walter Tanaka Tatekawa -----
C.C. 16.251.923 -----
Alain Cortesi Brunner -----
Cedula Extranjeria 215404 -----
a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

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

Barranquilla, 29 de Octubre de 2014 Hr:11:51:35



***** Pag. 7

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,815 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las
facultades otorgadas por los Estatutos Sociales, me permito -----
manifestarles que confiero poder especial, amplio y suficiente a
GETHEL MORENO ROMERO, identificada con C.C.32.689.958, para que ----
en nombre y representación de la sociedad, realice operaciones de
carácter Financiero con la firma conjunta de un(1)miembro del Grupo
A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin ----
perjuicios de las facultades otorgadas anteriormente a algunos de
los funcionarios e inscritas en la Cámara de Comercio de esta -----
ciudad, como determino: -----

GRUPO A -----

1. Monica De Hart De Ochoa -----

C.c. No. 32.676.025 -----

2. Javier Otero Arteaga -----

C.C. No. 91.263.993 -----

3. Gethel Moreno Romero -----

C.C. No.32.689.958 -----

GRUPO B -----

Marcela carvajalino Pagano -----

C.C. 22.579.748 -----

Walter Tanaka Tatekawa -----

C.C. 16.251.923 -----

Alain Cortesi Brunner -----

Cedula Extranjeria 215404 -----

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,816 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las
facultades otorgadas por los Estatutos Sociales, me permito -----
manifestarles que confiero poder especial, amplio y suficiente a

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

MARCELA CARVAJALINO PAGANO, identificada con C.C.22.579.748, para que en nombre y representación de la sociedad, realice operaciones de carácter Financiero con la firma conjunta de un(1)miembro del Grupo A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin perjuicios de las facultades otorgadas anteriormente a algunos de los funcionarios e inscritas en la Cámara de Comercio de esta ciudad, como determino: -----

GRUPO A -----

1. Monica De Hart De Ochoa -----

C.C. No. 32.676.025 -----

2. Javier Otero Arteaga -----

C.C. No. 91.263.993 -----

3. Gethel Moreno Romero -----

C.C. No.32.689.958 -----

GRUPO B -----

Marcela carvajalino Pagano -----

C.C. 22.579.748 -----

Walter Tanaka Tatekawa -----

C.C. 16.251.923 -----

Alain Cortesi Brunner -----

Cedula Extranjeria 215404 -----

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,817 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las facultades otorgadas por los Estatutos Sociales, me permito -----
manifestarles que confiero poder especial, amplio y suficiente a WALTER TANAKA TATEKAWA, identificado con C.C.16.251.923, para que en nombre y representación de la sociedad, realice operaciones de carácter Financiero con la firma conjunta de un(1)miembro del Grupo A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin -----
perjuicios de las facultades otorgadas anteriormente a algunos de los funcionarios e inscritas en la Cámara de Comercio de esta ciudad, como determino: -----

GRUPO A -----

1. Monica De Hart De Ochoa -----

C.C. No. 32.676.025 -----

2. Javier Otero Arteaga -----

C.C. No. 91.263.993 -----

3. Gethel Moreno Romero -----

C.C. No.32.689.958 -----

GRUPO B -----

Marcela carvajalino Pagano -----

C.C. 22.579.748 -----

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

Barranquilla, 29 de Octubre de 2014 Hr:11:51:35



***** Pag. 8

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

Walter Tanaka Tatekawa -----
 C.C. 16.251.923 -----
 Alain Cortesi Brunner -----
 Cedula Extranjeria 215404 -----
 a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

C E R T I F I C A

Que por Documento Privado del 07 de Mayo de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 01 de Junio de 2012 bajo el Nro 4,818 del libro respectivo,-----
 consta que el señor RUBEN MINSKI GONTOVNIK, identificado con -----
 C.C.7.463.982 de Barranquilla, en mi condición de Representante ----
 Legal y/o Presidente de la sociedad PROCAPS S.A., conforme a las
 facultades otorgadas por los Estatutos Sociales, me permito -----
 manifestarles que confiero poder especial, amplio y suficiente a
 ALAIN CORTESI BRUNNER, identificado con C.C.215404, para que -----
 en nombre y representación de la sociedad, realice operaciones de
 carácter Financiero con la firma conjunta de un(1)miembro del Grupo
 A y un(1)miembro del Grupo B o dos(2)miembros del Grupo A, sin ----
 perjuicio de las facultades otorgadas anteriormente a algunos de
 los funcionarios e inscritas en la Cámara de Comercio de esta -----
 ciudad, como determino: -----

GRUPO A -----

1. Monica De Hart De Ochoa -----

C.c. No. 32.676.025 -----

2. Javier Otero Arteaga -----

C.C. No. 91.263.993 -----

3. Gethel Moreno Romero -----

C.C. No.32.689.958 -----

GRUPO B -----

Marcela carvajalino Pagano -----

C.C. 22.579.748 -----

Walter Tanaka Tatekawa -----

C.C. 16.251.923 -----

Alain Cortesi Brunner -----

Cedula Extranjeria 215404 -----

a) Transferencias Bancarias entre cuentas de titularidad de PROCAPS S.A., hasta por la suma de USD 5000.000.00. b) Venta de cartera de PROCAPS S.A., hasta por la suma de USD 500.000.00. c) Suscripción de Contratos de Leasing, hasta por la suma de \$500.000.000.00.m.l.-----

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

C E R T I F I C A

Que por Documento Privado del 01 de Agosto de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 17 de Agosto de 2012 bajo el Nro 4,909 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía -----
No.7.463.982, expedida en Barranquilla, en mi condición de -----
Representante Legal y/o Presidente de la sociedad PROCAPS S.A., ----
conforme a las facultades otorgadas por los Estatutos Sociales, ----
todo lo cual consta en el Certificado de Existencia y -----
Representación Legal de la Cámara de Comercio de Barranquilla, que reposa en sus archivos e inscrito en su debida oportunidad, me -----
permito manifestarles que confiero poder especial, amplio y -----
suficiente a las, personas que se relacionan a continuación -----
funcionarios de la empresa, para que en nombre y representación de la sociedad, suscriban en forma Conjunta, Contratos de Suministro de Mercancías y Servicios con Entidades Oficiales; hasta por la ----
suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE -----
NORTEAMERICA (USD800.000.00). La conformación de estos dos nuevos Grupos A y B, reemplazaran a los funcionanos integrantes de los ----
Grupds A y B, que actualmente ss encuentran inscritos en la Cámara de Comereio de Barranquilla, con las mismas facultades -----
anteriormente determinada, como relaciono seguidamente: Del grupo A: 1. RODRIGO PIERNAGORDA SÁENZ C.C. No. 80.268.687, expedida en Bogotá.-----

C E R T I F I C A

Que por Documento Privado del 01 de Agosto de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 17 de Agosto de 2012 bajo el Nro 4,910 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía -----
No.7.463.982, expedida en Barranquilla, en mi condición de -----
Representante Legal y/o Presidente de la sociedad PROCAPS S.A., ----
conforme a las facultades otorgadas por los Estatutos Sociales, ----
todo lo cual consta en el Certificado de Existencia y -----
Representación Legal de la Cámara de Comercio de Barranquilla, que reposa en sus archivos e inscrito en su debida oportunidad, me -----
permito manifestarles que confiero poder especial, amplio y -----
suficiente a las, personas que se relacionan a continuación -----
funcionarios de la empresa, para que en nombre y representación de la sociedad, suscriban en forma Conjunta, Contratos de Suministro de Mercancías y Servicios con Entidades Oficiales; hasta por la ----
suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE -----
NORTEAMERICA (USD800.000.00). La conformación de estos dos nuevos Grupos A y B, reemplazaran a los funcionanos integrantes de los ----
Grupds A y B, que actualmente ss encuentran inscritos en la Cámara de Comereio de Barranquilla, con las mismas facultades -----
anteriormente determinada, como relaciono seguidamente: Del grupo A: 2. RICARDO DORADO HURTADO C.C. No.79.715.772, expedida en Bogotá.

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

Barranquilla, 29 de Octubre de 2014

Hr:11:51:35



***** Pag. 9

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

C E R T I F I C A

Que por Documento Privado del 01 de Agosto de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 17 de Agosto de 2012 bajo el Nro 4,911 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía -----
No.7.463.982, expedida en Barranquilla, en mi condición de -----
Representante Legal y/o Presidente de la sociedad PROCAPS S.A., ----
conforme a las facultades otorgadas por los Estatutos Sociales, ----
todo lo cual consta en el Certificado de Existencia y -----
Representación Legal de la Cámara de Comercio de Barranquilla, que reposa en sus archivos e inscrito en su debida oportunidad, me ----
permito manifestarles que confiero poder especial, amplio y -----
suficiente a las, personas que se relacionan a continuación -----
funcionarios de la empresa, para que en nombre y representación de la sociedad, suscriban en forma Conjunta, Contratos de Suministro de Mercancías y Servicios con Entidades Oficiales; hasta por la ----
suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE -----
NORTEAMERICA (USD800.000.00). La conformación de estos dos nuevos Grupos A y B, reemplazarán a los funcionarios integrantes de los ----
Grupos A y B, que actualmente se encuentran inscritos en la Cámara de Comercio de Barranquilla, con las mismas facultades -----
anteriormente determinada, como relaciono seguidamente: Del grupo A: 3. DAVID LECLERCQ LARRARTE C.C. No. 79.154.988, expedida en ----
Bogotá.-----

C E R T I F I C A

Que por Documento Privado del 01 de Agosto de 2012, otorgado en Barranquilla inscrito en esta Cámara de Comercio, el 17 de Agosto de 2012 bajo el Nro 4,912 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, varón, mayor de edad, de ésta vecindad, identificado con la cédula de ciudadanía -----
No.7.463.982, expedida en Barranquilla, en mi condición de -----
Representante Legal y/o Presidente de la sociedad PROCAPS S.A., ----
conforme a las facultades otorgadas por los Estatutos Sociales, ----
todo lo cual consta en el Certificado de Existencia y -----
Representación Legal de la Cámara de Comercio de Barranquilla, que reposa en sus archivos e inscrito en su debida oportunidad, me ----
permito manifestarles que confiero poder especial, amplio y -----
suficiente a las, personas que se relacionan a continuación -----
funcionarios de la empresa, para que en nombre y representación de la sociedad, suscriban en forma Conjunta, Contratos de Suministro de Mercancías y Servicios con Entidades Oficiales; hasta por la ----

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE -----
NORTEAMERICA (USD800.000.00). La conformación de estos dos nuevos
Grupos A y B, reemplazaran a los funcionanos integrantes de los ----
Grupds A y B, que actualmente ss encuentran inscritos en la Cámara
de Comereio de Barranquilla, con las mismas facultades -----
anteriormente determinada, como relaciono seguidamente: Del grupo
B: 1. SANDRA BIBIANA MALLUNGO BENITEZ C.C. No. 51.853.314, expedida
en Bogotá.-----

C E R T I F I C A

Que por Documento Privado del 01 de Agosto de 2012, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 17 de Agosto
de 2012 bajo el Nro 4,913 del libro respectivo,-----
consta que el señor RUBEN MINSKI GONTOVNIK, varón, mayor de edad,
de ésta vecindad, identificado con la cédula de ciudadanía -----
No.7.463.982, expedida en Barranquilla, en mi condición de -----
Representante Legal y/o Presidente de la sociedad PROCAPS S.A., ----
conforme a las facultades otorgadas por los Estatutos Sociales, ----
todo lo cual consta en el Certificado de Existencia y -----
Representación Legal de la Cámara de Comercio de Barranquilla, que
reposa en sus archivos e inscrito en su debida oportunidad, me ----
permito manifestarles que confiero poder especial, amplio y -----
suficiente a las, personas que se relacionan a continuación -----
funcionarios de la empresa, para que en nombre y representación de
la sociedad, suscriban en forma Conjunta, Contratos de Suministro
de Mercancías y Servicios con Entidades Oficiales; hasta por la ----
suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE -----
NORTEAMERICA (USD800.000.00). La conformación de estos dos nuevos
Grupos A y B, reemplazaran a los funcionanos integrantes de los ----
Grupds A y B, que actualmente ss encuentran inscritos en la Cámara
de Comereio de Barranquilla, con las mismas facultades -----
anteriormente determinada, como relaciono seguidamente: Del grupo
B: 2. EDGAR BELTRÁN ESTUPIÑAN C.C. No. 79.521.456, expedida en ----
Bogotá.-----

C E R T I F I C A

Que por Documento Privado del 06 de Dic/bre de 2012, otorgado en
Barranquilla inscrito en esta Cámara de Comercio, el 19 de Dic/bre
de 2012 bajo el Nro 4,982 del libro respectivo,-----
consta, que el señor RUBEN MINSKI GONTOVNIK, mayor de edad y vecino
de Barranquilla, identificado con la cédula de ciudadanía -----
No.7.463.982 de Barranquilla, en mi calidad de REPRESENTANTE LEGAL
y en condición de PRESIDENTE de C.I PROCAPS S.A. sociedad -----
domiciliada en Barranquilla y legalmente constituida; manifiesto
que confiero PODER ESPECIAL a la Doctora MARCELA CARVAJALINO PAGANO,
identificada con cédula de ciudadanía No.22.579.748 con las -----
siguientes facultades: Representar a C.I PROCAPS ante todo tipo de
autoridades administrativas y judiciales, en asuntos de naturaleza
cambiaria y fiscal, tales como: contestar e interponer demandas y
requerimientos, comparecer en juicios, pedir la practica de -----
pruebas, recibir notificaciones, interponer recursos y ejercer ----

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



***** Pag. 10

CAMARA DE COMERCIO
DE BARRANQUILLA

13*****

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----

NIT: 890.106.527-5.

acciones contencioso administrativas y de tutela, transigir, -----
 conciliar, recibir en nombre de la sociedad, desistir, sustituir y
 reasumir este mandato. para la celebracion de cualquier acuerdo ----
 conciliatorio o transaccional, judicial o extrajudicial, -----
 cualquiera que sea su cuantia, los apoderados deberan aportar la
 autorizacion escrita del representante legal de la sociedad. los
 apoderados podran presentar solicitudes de devolucion y/o -----
 compensacion de impuestos y recibir los pagos por devolucion de ----
 impuestos.-----

C E R T I F I C A

Que por Documento Privado del 06 de Dic/bre de 2012, otorgado en
 Barranquilla inscrito en esta Cámara de Comercio, el 19 de Dic/bre
 de 2012 bajo el Nro 4,983 del libro respectivo,-----
 consta, que el señor RUBEN MINSKI GONTOVNIK, mayor de edad y vecino
 de Barranquilla, identificado con la cédula de ciudadanía -----
 No.7.463.982 de Barranquilla, en mi calidad de REPRESENTANTE LEGAL
 y en condición de PRESIDENTE de C.I PROCAPS S.A. sociedad -----
 domiciliada en Barranquilla y legalmente constituida; manifiesto
 que confiero PODER ESPECIAL a la Doctora CRISTINA VIOLI -----
 FRANCESCHINI, identificada con cédula de ciudadanía No.22.463.716
 con las siguientes facultades: Representar a C.I PROCAPS ante todo
 tipo de autoridades administrativas y judiciales, en asuntos de ----
 naturaleza cambiaria y fiscal, tales como: contestar e interponer
 demandas y requerimientos, comparecer en juicios, pedir la practica
 de pruebas, recibir notificaciones, interponer recursos y ejercer
 acciones contencioso administrativas y de tutela, transigir, -----
 conciliar, recibir en nombre de la sociedad, desistir, sustituir y
 reasumir este mandato. para la celebracion de cualquier acuerdo ----
 conciliatorio o transaccional, judicial o extrajudicial, -----
 cualquiera que sea su cuantia, los apoderados deberan aportar la
 autorizacion escrita del representante legal de la sociedad. los
 apoderados podran presentar solicitudes de devolucion y/o -----
 compensacion de impuestos y recibir los pagos por devolucion de ----
 impuestos.-----

C E R T I F I C A

Que por Documento Privado del 01 de Agosto de 2012, otorgado en
 Barranquilla inscrito en esta Cámara de Comercio, el 17 de Agosto
 de 2012 bajo el Nro 4,913 del libro respectivo,-----
 consta que el señor RUBEN MINSKI GONTOVNIK, varón, mayor de edad,
 de ésta vecindad, identificado con la cédula de ciudadanía -----
 No.7.463.982, expedida en Barranquilla, en mi condición de -----

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

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.

PROCAPS S.A.-----
NIT: 890.106.527-5.

Representante Legal y/o Presidente de la sociedad PROCAPS S.A., ----
conforme a las facultades otorgadas por los Estatutos Sociales, ----
todo lo cual consta en el Certificado de Existencia y -----
Representación Legal de la Cámara de Comercio de Barranquilla, que
reposa en sus archivos e inscrito en su debida oportunidad, me ----
permito manifestarles que confiero poder especial, amplio y -----
suficiente a las, personas que se relacionan a continuación -----
funcionarios de la empresa, para que en nombre y representación de
la sociedad, suscriban en forma Conjunta, Contratos de Suministro
de Mercancías y Servicios con Entidades Oficiales; hasta por la ----
suma de OCHOCIENTOS MIL DOLARES DE LOS ESTADOS UNIDOS DE -----
NORTEAMERICA (USD800.000.00). La conformación de estos dos nuevos
Grupos A y B, reemplazaran a los funcionanos integrantes de los ----
Grups A y B, que actualmente ss encuentran inscritos en la Cámara
de Comereio de Barranquilla, con las mismas facultades -----
anteriormente determinada, como relaciono seguidamente: Del grupo
B: 3. LILIANA BENAVIDES BUITRAGO C.C. No. 52.250.516, expedida en
Bogotá.-----

C E R T I F I C A

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

C E R T I F I C A

Que su última Renovación fue el: 31 de Marzo de 2014.

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

C E R T I F I C A

De conformidad con lo establecido en el Código de Procedimiento
Administrativo y de lo Contencioso y de la Ley 962 de 2005, los
Actos Administrativos de Registro aquí certificados quedan en firme
Diez (10) días hábiles después de la fecha de inscripción, siempre
que no sean objeto de recursos.



Señor Director,
 DIRECCIÓN DE NUEVAS CREACIONES
 Superintendencia de Industria y Comercio
 E. S. D.

Referencia : Expediente N° 14 167105
 Asunto : Oposición a la solicitud de patente de Invención titulada
 "COMPRIMIDO ANTIÁCIDO"
 Solicitante : GLAXOSMITHKLINE LLC.
 Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
 N° 702 del 11 de Agosto de 2014

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

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará

más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular *carbonato de calcio*. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 31 de julio de 2014, reivindicando prioridad bajo la solicitud US201261594055P del 2012-02-02; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 702 del 11 de Agosto de 2014, cuya publicación internacional corresponde a la WO2013116477 (A1) del 2013-08-08.

2.2. La solicitud colombiana 14 167105 objeto de la presente oposición se refiere a un comprimido oral antiácido que comprende al menos aproximadamente 60% en peso de carbonato de calcio granulado directamente compresible y un saporífero intenso. El comprimido puede tener una dureza de al menos aproximadamente 22 unidades Strong-Cobb y el comprimido puede tener una masa de entre aproximadamente 500 mg y aproximadamente 1.000 mg. Los comprimidos de la presente invención reducen o eliminan los síntomas de la acidez estomacal y también refrescan el aliento.

2.3. En primera instancia, se debe advertir que las reivindicaciones también se refieren a usos y métodos de tratamiento y no sólo a la composición farmacológica o a un método de fabricación mediante la cual se obtenga un producto tangible y según la legislación, decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *“Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento (...)”*, los usos no están contemplados como patentables; y, Artículo 20.- *“No serán patentables (...) d) los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales”*. Solo serán patentables los productos o procedimientos. Por lo tanto a luz de la norma, dicha materia referente métodos de tratamiento no sería patentable.

2.4. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: US5880106 publicada el 9 de marzo de 1999.
- D2: US20020150617 publicada el 17 de Octubre de 2002.

2.5. Ahora bien, el documento D1, se refiere a formulaciones de dosificación oral para derivados nucleósidos didesoxi de purina lábiles en medio ácido, tales como ddA, ddI, y ddG, que han desarrollado mediante la incorporación de sistemas de tamponamiento insolubles en agua seleccionados en la formulación. Según D1, estas formulaciones proporcionan unidades de dosificación de masa en forma de cómoda, agradable al paladar masticable en comprimidos dispersables o una bolsita de polvo seco que comprenden un agente antiácido de magnesio insoluble o bien carbonato de sodio o calcio dihidroxialuminio carbonato. D1 enseña una tableta oral antiácido (pastilla oral antiácido, Col. 3, líneas 22-43; Col. 5, líneas 5-15; y, reivindicación 1) que comprende: carbonato de calcio (carbonato de calcio, reivindicación 1; Col. 9, línea 35-Col. 10, línea 46); y un aroma intenso (un aromatizante, tal como gaulteria, Col. 6, líneas 10-14; y, reivindicaciones 1 y 22); en el que el comprimido tiene una dureza de al menos aproximadamente 22 Unidades Strong Cobb (tabletas se compactaron a una dureza de 16 a 24 Strong-Cobb, Col. 9, líneas 9-13).

2.6. Por otro lado, la anterioridad D2 proporciona un método de hacer composiciones de comprimidos que están sustancialmente libres de excipientes. Este documento revela al menos aproximadamente 60% en peso de carbonato de calcio granulado directamente comprimible (0,5 a 97 por ciento en peso de uno o más compuestos terapéuticos adicionales, es decir, el tercer compuesto terapéutico, que puede ser

carbonato de calcio OC, es decir, carbonato de calcio directamente comprimible:

Párrafos: [0025] - [0026]; [0072]; [0107] - [0108], Tabla 7; y, reivindicaciones 1 y 12).

2.7. Por tanto, es evidente para un experto normal en la técnica en el momento de la invención, modificar el documento D1 para usar la cantidad deseada de carbonato de calcio con un relleno mínimo, tal como carbonato cálcico directamente compresible, según lo enseñado por D2. La motivación para hacerlo sería lograr la capacidad óptima antiácida de la tableta (D1: Col. 3, líneas 45-56; Col. 4, líneas 36-54; Col. 5, líneas 48-60) con un mínimo de excipientes para reducir el peso y el volumen de las tabletas (D2: Párrafos. [0069] - [0071]). D1, no revela explícitamente en el que el comprimido tiene una masa de entre aproximadamente 500 mg y aproximadamente 1000 mg. Sin embargo, D2 enseña que el comprimido tiene una masa de entre aproximadamente 500 mg y aproximadamente 1000 mg (la composición se compacta en una tableta con una masa de 100 mg a 2000 mg, Párrafos: [0028]; y, [0069]). Por tanto es evidente para un experto normal en la técnica en el momento de la invención modificar D1 para limitar la cantidad de excipientes con el fin de compactar la tableta a la masa deseada, según lo enseñado en D2. La motivación para hacerlo sería la de formar una tableta de peso óptimo y el volumen que tiene las propiedades deseadas, tales como resistencia, dureza, desintegración y liberación de compuestos terapéuticos tras la administración (D1: Párrafos [0028], [0065]; y, [0070] - [0071]). De igual forma, D1 enseña que hay al menos aproximadamente 70% en peso de carbonato de calcio granulado directamente comprimible (0,5 a 97 por ciento en peso de uno o más compuestos terapéuticos adicionales, es decir, la tercera compuesto terapéutico, que puede ser OC carbonato de calcio, es decir, directamente compresible, párrafos: [0025] - [0026]; [0072]; [0107] - [0108], Tabla 7; reivindicaciones 1 y 12).

2.8. Como se evidencia, en vista de lo revelado en D1 con las modificaciones presentadas en D2 un experto en la materia, podría obviamente llegar a conformar la forma oral según la presente solicitud, por lo que carece evidentemente de altura inventiva.

2.9. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 14 167105 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.8.1 CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 2 de febrero de 2012, un experto en la materia habría podido deducir de manera obvia, el hecho de modificar D1 para limitar la cantidad de excipientes con el fin de compactar la tableta a la masa deseada, según lo enseñado en D2 para llegar a una tableta de peso óptimo y el volumen que tiene las propiedades deseadas, tales como resistencia, dureza, desintegración y liberación de compuestos terapéuticos tras la administración, sobre lo cual busca protección en el presente capítulo reivindicatorio.

2.8.2 CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman un método de tratamiento y estos no son aplicables industrialmente porque primero no se obtiene un producto o proceso; y segundo no es reproducible o repetible a escala industrial. Por lo tanto, el objeto de la presente invención referido a métodos de tratamiento, no cumple con el requisito de la aplicación industrial.

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

aplicación industrial.". La solicitud pretendida no cumple con dos de los tres requisitos de patentabilidad.

2.10 Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada "*COMPRIMIDO ANTIÁCIDO*", cuyo titular **GLAXOSMITHKLINE LLC.**, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 702 del 11 de Agosto de 2014.

3. PRUEBAS

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

- D1: US5880106 publicada el 9 de marzo de 1999.
- D2: US20020150617 publicada el 17 de Octubre de 2002.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Artículo 45 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.2. En las demás normas concordantes.

5. ANEXOS

Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de **PROCAPS S.A.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US5880106 publicada el 9 de marzo de 1999.
 - D2: US20020150617 publicada el 17 de Octubre de 2002.

6. NOTIFICACIONES

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

Señor director,

ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.