



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: 11 160.575

Solicitante: ICEUTICA PTY LTD

Apoderado: DILIA MARIA RODRIGUEZ

Título de la Nueva Creación: PRODUCCIÓN DE MONOPARTÍCULAS ENCAPSULADAS EN FRACCIONES DE ALTO VOLUMEN

Gaceta: 647

2. Datos del Opositor

☐ Persona Natural ☒ Persona Jurídica
PROCAPS S.A.

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 8 folios (obligatorios indicar cuántos).
- ☒ Anexo de fundamentos de la oposición. Se anexan 13 folios (obligatorios indicar cuántos)
- ☒ Copias para traslado.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

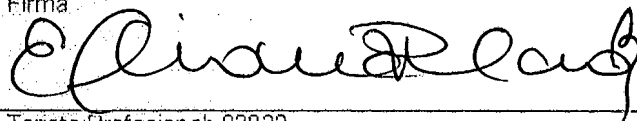
6. Firma

Nombre del Firmante

ELIANA ISaura MORENO BOHORQUEZ

CC. 51.975.664

Firma



Tarjeta Profesional: 83823

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



RECIBO DE CAJA

No. 12 - 0093738

Bogotá D.C., Septiembre 12 de 2012 - 14:47:30

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	144688353	29/08/2012	3.780.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12	MARCAS Y LEMAS COMERCIALES
			315.000.00	315.000.00
				\$315.000.00

SON: **TRESCIENTOSQUINCE MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-160575-00003-0000

Fecha: 2012-09-12 16:13:38 Dep. 2020 DIR. NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 34

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

Web: www.slc.gov.co e-mail: info@slc.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

Septiembre 12 de 2012 - 14:47:31

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

Referencia : Expediente N° 11 160575
Asunto : Oposición a la solicitud de patente de Invención titulada
"PRODUCCIÓN DE MONOPARTÍCULAS
ENCAPSULADAS EN FRACCIONES DE ALTO
VOLUMEN"
Solicitante : ICEUTICA PTY LTD.
Opositora : PROCAPS S.A.

Publicada en la Gaceta de la Propiedad Industrial
N° 647 del 29 de junio de 2012

Yo, **ELIANA ISAURA MORENO BOHORQUEZ**, 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, 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 "**PRODUCCIÓN DE MONOPARTÍCULAS ENCAPSULADAS EN FRACCIONES DE ALTO VOLUMEN**", cuyo titular es **ICEUTICA PTY LTD.**, y

Carrera 13 N° 119-95, Of. 104 Tel. (571) 2 13 12 13 - 6 20 50 21 - Fax. (571) 6 12 19 79
E-mail: negocios@optimum-co.com - www.optimum-co.com
Bogotá Colombia

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 **MONOPARTÍCULAS ENCAPSULADAS**. 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 23 de noviembre de 2011, reivindicando prioridad bajo la solicitud US20090172278 del 2009-04-24; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° **647 del 29 de junio de 2012**, cuya publicación internacional corresponde a la WO2010121320 del 2010-10-28.

2.2. La solicitud colombiana 11 160575 objeto de la presente oposición, se refiere a se refiere a métodos para la producción de partículas de un material biológicamente activo al usar procesos de molienda en seco así como a composiciones que comprenden tales materiales, medicamentos producidos al usar dichos materiales biológicamente activos en forma particulada y/o composiciones, y a métodos de tratamiento de un animal, incluyendo el hombre, al usar una cantidad terapéuticamente efectiva de dichos materiales biológicamente activos administrados por medio de dichos medicamentos.

2.3. En primera instancia, se debe advertir que las reivindicaciones se refieren a 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 a 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: US2008254128 publicada el 16 de octubre de 2008.

2.5. Ahora bien, el documento D1 proporciona un método de precipitación continua y aislamiento de una forma amorfa particulada sólida de 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyryl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide que tiene propiedades físicas controladas y proporciona también formulaciones farmacéuticas que comprenden el compuesto precipitado. De manera particular, dicho documento D1 describe la molienda en seco de una mezcla granulada que tiene 57% en peso de una sustancia activa en celulosa microcristalina, lactosa monohidrato, croscarmelosa sódica, almidón pregelatinizado y lauril sulfato de sodio. Finalmente, si bien no hay ninguna descripción de tamaños de partículas o tiempos de molienda es de esperarse que teniendo el 57% en peso se tenga también una fracción de volumen de más del 25%.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 11 160575 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.

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

2.8. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *“Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.”*. A la fecha de prioridad, 24 de abril de 2009 ya era conocido, pues como se demostró, eran parte del arte anterior con base en el documento D1, métodos para la producción de partículas de un material biológicamente activo al usar procesos de molienda en seco así como a composiciones que comprenden tales materiales, medicamentos producidos al usar dichos materiales biológicamente activos en forma particulada y/o composiciones; sobre lo cual busca protección en el capítulo reivindicatorio.

2.8.1. 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 los métodos 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 los 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 ***“PRODUCCIÓN DE MONOPARTÍCULAS ENCAPSULADAS EN FRACCIONES DE ALTO VOLUMEN”***, cuyo titular es ICEUTICA PTY LTD., solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 647 del 29 de junio de 2012.

3. PRUEBAS

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

- D1: US2008254128 publicada el 16 de octubre de 2008.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.
- 4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.
- 4.3. En las demás normas concordantes.

5. ANEXOS

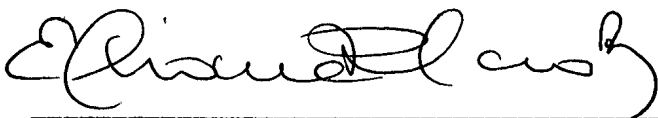
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

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: US2008254128 publicada el 16 de octubre de 2008.

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



US 20080254128A1

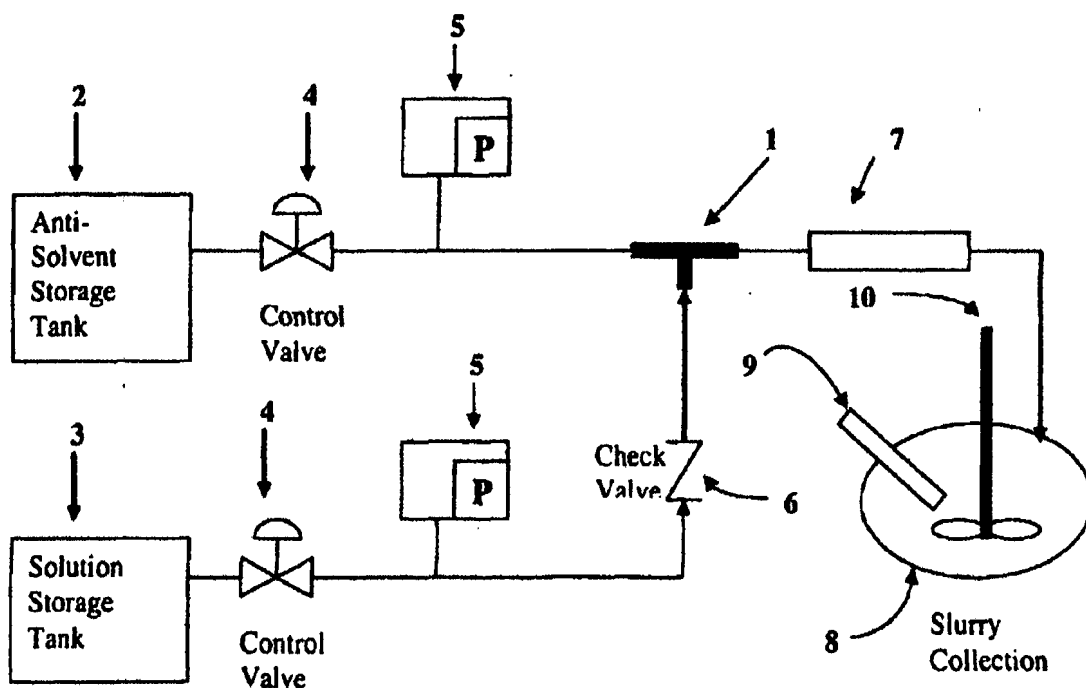
(19) **United States**(12) **Patent Application Publication**
Zarkadas et al.(10) **Pub. No.: US 2008/0254128 A1**(43) **Pub. Date: Oct. 16, 2008**(54) **PROCESS FOR THE PRECIPITATION AND ISOLATION OF 6,6-DIMETHYL-3-AZA-BICYCLO [3.1.0] HEXANE-AMIDE COMPOUNDS BY CONTROLLED PRECIPITATION AND PHARMACEUTICAL FORMULATIONS CONTAINING SAME**(76) **Inventors:** **Dimitrios Zarkadas**, Fanwood, NJ (US); **Vincenzo Liotta**, Glen Ridge, NJ (US); **Christopher Stanley Pridgen**, Union City, NJ (US); **Wing-kee Phillip Cho**, Princeton, NJ (US); **Zhihui Qiu**, Bridgewater, NJ (US)**Correspondence Address:**
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530 (US)(21) **Appl. No.: 12/080,989**(22) **Filed: Apr. 8, 2008****Related U.S. Application Data**

- (63) Continuation-in-part of application No. 11/789,915, filed on Apr. 26, 2007.
- (60) Provisional application No. 60/795,753, filed on Apr. 28, 2006, provisional application No. 60/796,717, filed on May 2, 2006, provisional application No. 60/796,490, filed on May 1, 2006, provisional application No. 60/873,877, filed on Dec. 7, 2006.

Publication Classification

- (51) **Int. Cl.**
A61K 9/16 (2006.01)
C07D 209/52 (2006.01)
A61K 31/403 (2006.01)
- (52) **U.S. Cl.** 424/489; 548/515; 514/412
- (57) **ABSTRACT**

The present invention provides a method of continuous precipitation and isolation of an amorphous solid particulate form of 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide having controlled physical properties. The present invention provides also pharmaceutical formulations comprising the precipitated compound.



PROCESS FOR THE PRECIPITATION AND ISOLATION OF 6,6-DIMETHYL-3-AZA-BICYCLO[3.1.0]HEXANE-AMIDE COMPOUNDS BY CONTROLLED PRECIPITATION AND PHARMACEUTICAL FORMULATIONS CONTAINING SAME

CROSS-REFERENCE TO RELATED APPLICATIONS

Fundamental de la invención en las normas de la OMC

[0001] The present application is a continuation-in-part of U.S. Ser. No. 11/789,915, filed Apr. 26, 2007, which in turn is based on and claims the priority of each of U.S. Provisional Application Nos. 60/795,753 filed Apr. 28, 2006, 60/796,717 filed May 2, 2006, 60/796,490 filed May 1, 2006, and 60/873,877 filed Dec. 7, 2006, each of which is incorporated herein by reference in its entirety.

4.2. Artículo 42 de la Decisión 486 de la OMC

FIELD OF THE INVENTION

[0002] The present invention is directed to a process for precipitation and isolation of compounds having therapeutic properties, more particularly, precipitation and isolation of 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide and granular pharmaceutical formulations containing the same.

BACKGROUND OF THE INVENTION

[0003] Identification of any publication in this section or any section of this application is not an admission that such publication is prior art to the present invention.

[0004] One method of providing a pharmaceutical compound in a solid form is to precipitate the compound from a solution by combining an anti-solvent and a solution of a compound to be precipitated (solvent/anti-solvent precipitation processes). Generally, when preparing a precipitate using solvent/anti-solvent precipitation processes, the characteristics of the precipitated material show increasing sensitivity to the presence of concentration gradients created during solution and anti-solvent mixing with increasing rapidity of particle formation upon combining the solution and anti-solvent. Examples of the precipitated product characteristics which can be affected by the presence of concentration gradients in a solvent/anti-solvent precipitation process include the range of primary particle sizes provided by the precipitation process, the size, bulk surface area, and bulk density of precipitated particles (agglomerates of primary particles), and the amount of solvent included in the precipitated particles.

[0005] Solvent/anti-solvent precipitation processes are typically carried out in a batch process. In general, batch processes are run by introducing, at a slow rate under mixing conditions, small aliquots of a solution of the compound to be precipitated into a tank containing the anti-solvent. It is common in batch processes of this type for the mixing shear in the anti-solvent tank to be insufficient to provide mixing of the anti-solvent and the solution that is sufficiently free from concentration gradients that the process provides particles of consistent and controlled size range with low solvent inclusion.

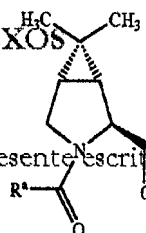
[0006] Solvent/anti-solvent precipitation processes in which nucleation rate is on the same order of magnitude as, or faster than, the rate of mixing are said to be mixing-controlled

precipitated particle materials some workers have adopted methods which include high-velocity impinging of substantially opposed streams of solvent and anti-solvent to provide better control of particle size range and maintain low solvent inclusion in the precipitated material, see for example U.S. Pat. No. 5,314,506 to Midler et al. (the '506 patent), and U.S. Pat. No. 6,558,435 to Am-Ende et al., each of which teaches producing crystals of controlled size by utilizing substantially diametrically opposed impinging jets of solution and anti-solvent to produce high intensity micromixing and precipitate crystals of the dissolved compound. U.S. Pat. No. 6,302,958 to Lindrud et al., teaches utilizing the impinging streams as taught in the '506 patent and in addition utilizing an ultrasonic probe placed in the zone of impingement to increase the mixing rate to a point at which the rate of homogenization of the admixed liquids is on a time scale smaller than the crystal nucleation time within the mixing zone. Each of these solutions to mixing-controlled precipitation requires the use of precise mechanisms and relies on precise control of fluid dynamics to control the physical aspects of the crystalline solids precipitated.

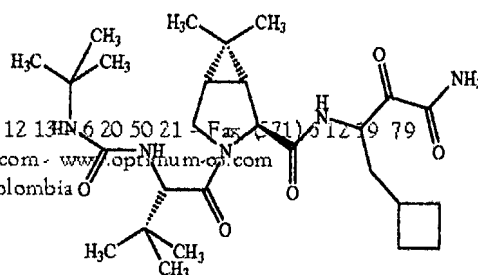
[0007] U.S. Pat. No. 7,012,066 to Saskena, et al. (the '066 patent) describes 6,6-dimethyl-3-aza-bicyclo[3.1.0]-hexane-amide compounds of Formula A,

Formula A

5. ANEXOS



wherein R^a represents the moieties described in the '066 patent as R₁, Z, R₁W and Y and R^b represents the moieties described in the '066 patent as methylene substituted by R₁ and R₂. One specific example of the compounds described in the '066 patent is 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide (the compound of Formula B, see the '066 patent at col. 113, Example XXIV (cols. 448 to 451) and col. 1259). These compounds have desirable properties as hepatitis C virus (HCV) protease inhibitors in the treatment of HCV infections.



[0008] When incorporating such compounds into a medicament for the treatment or prevention of conditions amenable to HCV protease inhibitor therapy, it is desirable to provide an active compound used in a pharmaceutical formulation (API), for example, a compound of Formulae A or B, in a highly pure form which has consistent physical properties, for example, in the form of an agglomerated particulate material having an average size in the micron range, with a narrow particulate size distribution, consistent bulk density, low amounts of included solvent, and a sharply defined melting point. It is preferable if a compound can be crystallized as the dynamics of crystallization can be employed to insure high purity and utilized to insure uniform physical properties. Attempts to provide the compound of Formula B in a crystalline form have not met with success.

[0009] In the provision of compounds suitable for pharmaceutical use it is common practice to purify and isolate pharmaceutically active compounds by precipitating the solid compound from a solution of the compound. One common precipitation method, termed herein "the solution/anti-solvent method", is carried out by mixing a solution of the desired compound into a sufficient amount of an anti-solvent to provide a solvent/anti-solvent mixture in which the desired compound has reduced solubility. Accordingly, upon mixing a solution of the desired compound and an anti-solvent, the desired compound forms primary particles which aggregate and precipitate from the combined liquids forming a slurry comprising precipitated particles and the combined solvent and anti-solvent liquid.

[0010] When the solvent/anti-solvent method is applied to the provision of the compound of Formula B in a batch crystallizer, there is precipitated an amorphous, particulate material which has highly varied primary particle size and a wide range in size of agglomerates, necessitating secondary classification of the particulate material produced from the precipitation process. Moreover, the precipitation product of the compound of Formula B provided from a batch crystallizer by the solution/anti-solvent method yields a precipitated material which retains a widely varied amount of solvent, batch to batch, and often provides a product which either requires a prolonged drying time to drive off the excess included solvent or has the form of a gum rather than a particle form, and accordingly is unusable.

OBJECTIVES AND SUMMARY OF THE INVENTION

[0011] In view of the foregoing, what is needed is a method of providing a compound of Formula A, for example, 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide, the compound of Formula B, in a solid, high purity, precipitated particle form and/or agglomerated particulate form, the method consistently yielding solids having a narrow size range, for example, particle sizes of from about 200 nm to about 300 nm, a narrow chord length range for agglomerated particulate and precipitated particles, and in addition provides the desired level of control over the quantity of included solvent. These and other objectives and/or advantages are provided by the present invention.

[0012] Accordingly, in one aspect of the present invention there is disclosed a method of precipitating a compound of Formula A, for example, 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-

carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide (the compound of Formula B) in an amorphous, solid particulate form comprising primary particles within a size range of from about 200 nm to about 300 nm, the method comprising introducing a stream of a solution of the compound of Formula B into a stream of an anti-solvent for the compound of Formula B under controlled turbulent flow conditions. In some embodiments it is preferred to maintain the Reynolds number (Re) of the solution stream at a value which is at least sufficient to provide turbulent flow, for example, a value of at least about 2,000, more preferably a value of at least about 5,500, more preferably at value of at least about 10,000. In some embodiments it is preferred to maintain the Reynolds number of the anti-solvent stream at a value of at least about 9,000, preferably at a value of at least about 15,000, more preferably at a value of at least about 20,000. In some embodiments it is preferred to combine the streams absent any co-current component. In some embodiments it is preferred to combine solvent stream with an anti-solvent stream at an angle substantially 90 degrees with respect to the anti-solvent stream. In some embodiments it is preferred to combine the streams absent any stream impinging component.

[0013] In some embodiments the inventive method comprises utilizing a stream of a solution of Formula B wherein the Reynolds number of the solution stream is maintained at a value of at least about 5,500, and the volumetric ratio of the stream of solvent and the stream of anti-solvent is from about 1:15 to about 1:3 solution:anti-solvent, preferably about 1:4 solution:anti-solvent.

[0014] In some embodiments it is preferred to maintain the region of the equipment in which contact between the solution and anti-solvent occurs at a temperature of from about -25° C. to about +25° C., preferably from about -25° C. to about +20° C. Preferably, region of the equipment wherein contact between the solution and the anti-solvent occurs is maintained at a temperature of about -15° C. In some embodiments it is preferred to maintain the anti-solvent at a temperature of from about -25° C. to about +20° C., preferably at a temperature of about -20° C. In some embodiments it is preferred to maintain the solution of the compound of Formula B at a temperature of from about -10° C. to about +20° C., preferably at a temperature of about 0° C. In some embodiments the anti-solvent and solution are cooled to the desired temperature and the region of the equipment in which the solution and anti-solvent are combined, for example, a mixing Tee, is operated at ambient temperature.

[0015] In some embodiments preferably the solution of the compound of Formula B comprises methyl-tertiarybutyl-ether (MTBE) as a solvent. In some embodiments preferably the solution contains an amount of the compound of Formula B providing a solution having from about 80 mg/ml (0.15 M) to about 250 mg/ml (0.48 M) of the compound of Formula B, preferably from about 166 mg/ml to about 200 mg/ml of the compound of Formula B, more preferably about 166 mg/ml of the compound of Formula B. In some embodiments it is preferred for the solvent to be selected from methyl-tertiarybutyl-ether (MTBE) and a mixture of ethylacetate and MTBE. In some embodiments preferably the anti-solvent is n-heptane. In some embodiments it is preferred to substantially remove water from the solution prior to precipitation, for example, by drying the solution with a drying agent, distillation, or CUNO filtration. In some embodiments the

[0016] In some embodiments it is preferred to carry out the precipitation process by utilizing a continuously blended stream of solution and anti-solvent, forming a slurry of solvent, anti-solvent and precipitated particles (initial slurry). In some embodiments it is preferred to conduct the initial slurry from the region where the solution and anti-solvent are combined to a holding tank in which the initial slurry is collected. In some embodiments, optionally, a static mixer is disposed in the conduit between the blending region and holding tank through which the slurry is conducted. In some processes utilizing a continuously blended stream of solution and anti-solvent it is preferred to collect the precipitated solids by one or more techniques selected from decantation, filtration and centrifugation.

[0017] In some embodiments it is preferred to collect the slurry formed by combining streams of solution and anti-solvent in a holding tank, and additionally carry out a distillation step on the collected slurry.

[0018] In some embodiments it is preferred to remove an amount of liquid that provides a residual slurry having a volume which is from about 90 vol. % to about 25 vol. % of the initial slurry volume, more preferably to provide a volume of from about 90 vol. % to about 30 vol. % of the initial slurry volume, more preferably to provide a slurry volume which is about one third of the initial slurry volume.

[0019] In some embodiments the distillation step is carried out in a controlled pressure/temperature distillation regime to facilitate reproducible agglomeration of the precipitated solids (precipitated particles), thereby forming an agglomerated particulate of controlled chord length, bulk surface area, and bulk density. In some embodiments it is preferred to perform the distillation step under reduced atmosphere conditions, preferably under pressure conditions of greater than about -0.97 Bar gage (barg), at a temperature of less than about 32° C. In some embodiments it is preferred to distill off from about 18 vol % to about 22 vol % of the initial slurry volume at a temperature of less than about 30° C. In some embodiments it is preferred to distill off the first 10 vol % of the initial slurry volume at a temperature of less than about 26° C. In some embodiments it is preferred to distill off the first 8 vol % of the initial slurry volume at a temperature of less than about 25° C. In some embodiments it is preferred to distill off the first 6 vol % of the initial slurry volume at a temperature of less than about 23° C. In some embodiments it is preferred to distill off the first 4 vol % of the initial slurry volume at a temperature of less than about 22° C. In some embodiments it is preferred to distill off the first 2 vol. % of the initial slurry volume at a temperature of less than about 21° C.

[0020] In some embodiments, following concentration of the initial slurry, the process further comprises isolating the agglomerated particulate by filtration followed by washing the filter cake with aliquots of anti-solvent. In some embodiments it is preferred to wash the filter cake with n-heptane, equal in volume to about 4 times the volume of the filter cake. In some embodiments it is preferred to wash the filter cake with a mass of anti-solvent equal to the mass of the filter cake. In some embodiments it is preferred to wash the filter cake with 2 aliquots of antisolvent equal in mass of the filter cake. In some embodiments it is preferred to wash the filter cake with anti-solvent until the residual solvent level in the filter cake is less than from about 1 to about 1.5 wt. %.

[0021] In some embodiments, after washing the filter cake the process further comprises drying the isolated agglomer-

of from about 25° C. to about 45° C. for a period sufficient to reduce the total residual solvent to a value of less than about 1.0 wt. %, preferably less than about 0.8 wt. %.

[0022] In some embodiments it is preferred that the concentration of 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide (the compound of Formula B), the volumetric ratio of the stream of solution and anti-solvent, and the linear velocity of the combining streams are selected to produce a precipitate of the compound of Formula B having a primary particle of less than about 1.0 micron, a median precipitated particle size (aggregation of primary particles) of from about 1 micron to about 2.5 microns, preferably about 1.5 microns, a precipitated particle size distribution of from about 1 micron to about 50 microns and a level of included solvent of less than about 1 wt. %. In some embodiments it is preferred to select process conditions producing precipitated particles in the initial slurry having a bulk surface area of from about 16 m²/g to about 33 m²/g, preferably from about 25 m²/g to about 32.5 m²/g. In some embodiments it is preferred to select process conditions providing a slurry wherein the solids in the slurry have a softening point of from about 20° C. to about 50° C., preferably from about 25° C. to about 50° C. In some embodiments it is preferred to carry out a distillation step on the initially collected slurry under conditions yielding an agglomerated particulate having a bulk surface area range of from about 5 m²/g to about 12 m²/g. In some embodiments it is preferred to select distillation step conditions yielding an agglomerated particulate having a median bulk surface area of about 7 m²/g.

[0023] Another aspect of the present invention is the provision of a pharmaceutical formulation having a bulk density of from about 0.4 mg/ml to about 0.6 mg/ml, preferably a bulk density of about 0.47 mg/ml and a tapped density of about 0.64 mg/ml, and comprising the an agglomerated particulate prepared in accordance with the present invention. In some embodiments it is preferred for the granular pharmaceutical formulation to comprise up to 50 wt. % API comprising the compound of Formula B prepared in accordance with the process of the invention, preferably 50 wt. % API, up to 14 wt. % lactose monohydrate, preferably 14 wt. % lactose monohydrate, up to 6 wt % croscarmellose sodium, preferably 6 wt. % croscarmellose sodium, up to 10 wt. % microcrystalline cellulose, preferably 10 wt. % microcrystalline cellulose, up to 15 wt. % pregelatinized starch, preferably 15 wt. % pregelatinized starch, up to 6 wt. % sodium lauryl sulfate, preferably 3 wt. % sodium lauryl sulfate, and up to 2 wt. % magnesium stearate, preferably 2 wt. % magnesium stearate.

[0024] In some embodiments it is preferred to prepare a granular pharmaceutical formulation by a process comprising:

[0025] (a) forming a first granulate by a process comprising:

[0026] (i) blending an amount of the compound of Formula B prepared in accordance with the process of the invention (API) sufficient to provide up to 58 wt %, preferably 55.6 wt. %, of the first granulate, an amount of microcrystalline cellulose sufficient to provide up to 6.0 wt. %, preferably 5.6 wt. % of the first granulate, an amount of pregelatinized starch sufficient to provide up to 18 wt. %, preferably 16.6 wt. % of the first granulate, an amount of croscarmellose

3.3 wt. % of the first granulate, and an amount of lactose monohydrate sufficient to provide up to 16 wt. %, preferably 15.6 wt % of the first granulate, to provide a first dry-blended mixture;

[0027] (ii) granulating the mixture from step "a(i)" using a granulating fluid comprising an amount of sodium lauryl sulfate (SLS) sufficient to provide up to 6.6 wt %, preferably 3.3 wt. % of the first granulate dissolved in an amount of water equal to about seven times the weight of SLS,

[0028] (iii) wet-milling the granulate from step "ii" to provide a uniform granulate size;

[0029] (iv) drying the wet granulate prepared in step (iii) until the granulate displays a loss on drying (LOD) of less than 2.5 wt. %;

[0030] (b) milling the dried first granulate through a screen to provide a classified granulate;

[0031] (c) forming a second dry-blended mixture by blending the classified granulate from step "a(iv)" with an amount of microcrystalline cellulose sufficient to provide up to 6 wt %, preferably 5.1 wt % of the second dry-blended mixture and an amount of croscarmellose sodium sufficient to provide up to 6.2 wt. %, preferably 3.1 wt % of the second dry-blended mixture; and

[0032] (d) forming a granulate pharmaceutical formulation product by dry-blending the second dry-blended mixture with an amount of magnesium stearate sufficient to provide up to 3 wt %, preferably 2 wt. % of the granulate product.

[0033] In some embodiments it is preferred to provide a medicament in capsule dosage form by filling capsules with an amount of the granular pharmaceutical formulation prepared in accordance with the above-described process sufficient to provide a desired quantity of the API contained in the particulate formulation. In some embodiments it is preferred to prepare the first granulate using a high shear mixer/granulator for blending and granulation, a wet mill equipped with a screen having 0.375 inch holes, a fluid bed dryer and a dry mill equipped with a a screen having 0.040 inch holes. In some embodiments it is preferred to carry out dry-blending operations in a bin blender.

[0034] In some embodiments It is preferred to form the first granulate from a mixture made by dry-blend 40 Kg of the compound of Formula B (API), prepared in accordance with the above-described precipitation method and used as prepared, with 4.0 Kg of microcrystalline cellulose, 11.2 Kg of lactose monohydrate, 12.0 Kg of pregelatinized starch, and 2.4 Kg of croscarmellose sodium to make the first dry-blended mixture. In some embodiments it is preferred to provide a granulating fluid comprising 2.4 Kg of sodium lauryl sulfate dissolved in 48 Kg of water and to granulate the dry blended mixture until no free-flowing powder is observed. In some embodiments it is preferred to dry the granulate in a fluid bed dryer until it demonstrates a loss on drying of less than about 2.5 wt %. In some embodiments it is preferred to mill the dried granulate in a screen mill equipped with a 0.032 inch screen to provide a granular material having an average 32 mesh size. In some embodiments it is preferred to blend the dried, milled granulate with 4.0 Kg additional of microcrystalline cellulose and 2.4 Kg additional of croscarmellose sodium to provide a second dry-blended mixture, then blend 1.6 Kg of magnesium stearate with the second dry-blended mixture to provide the granular pharmaceutical

[0035] In some embodiments, optionally, aliquots of the granular pharmaceutical formulation described above are charged into gelatin capsules to provide a dosage form having the component weights shown in the table below (each dose having approximately 200 mg of API.

Constituent	Function	Concentration (mg/capsule)
Precipitate of Compound of Formula B ^c	Drug Substance	200
Microcrystalline Cellulose	Binder/Filler	40
Lactose Monohydrate	Filler	56
Croscarmellose Sodium	Disintegrant	24
Pregelatinized Starch	Binder	60
Sodium Lauryl Sulfate	Surfactant	12
Magnesium Stearate	Lubricant	8
Purified Water ^a	Processing Aid	(—) ^a
Capsule Net Fill Weight		400
Hard Gelatin Capsule ^b	Contain Capsule Fill	1 each

^aAdded for processing; evaporates during the manufacturing process,
^bNo. 0, blue, opaque, preservative-free, two-piece hard gelatin capsules,
^cWeight assumes 100% activity for precipitate - actual formulation weight adjusted upwards for lower activity.

[0036] Another aspect of the present invention is the provision of a dosage form comprising an amount of the granular pharmaceutical formulation comprising up to 58 wt. % API of the compound of Formula B, up to 6 wt. % microcrystalline cellulose, up to 18 wt. % pregelatinized starch, up to 4 wt. % croscarmellose sodium, up to 16 wt. % lactose monohydrate, and up to 6 wt. % sodium lauryl sulfate, further characterized by a bulk density of from about 0.4 g/ml to about 0.6 g/ml and wherein the particulate form of the API is an agglomerated particulate characterized by a bulk surface area of from about 5 m²/g to about 12 m²/g and a bulk density of from about 0.15 g/ml to about 0.19 g/ml, said dosage form further characterized by containing 800 mg of the API and exhibiting a C_{max} of 2106 at about 3.0 hours and an AUC of 7029 when a administered as a single dose.

[0037] In some embodiments it is preferred to provide the above-described pharmaceutical formulation by substituting for the above-described API of Formula B, one or more compounds selected from the compounds of Formulae I-XXVIII as described herein. Such formulations can be useful for inhibiting HCV protease and/or capthesin activity and have good dissolution characteristics to facilitate absorption of the compounds of Formulae I-XXVIII.

[0038] In some embodiments, it is preferred to select at least one HCV protease inhibitor from the group of HCV protease inhibitors referred to in the following documents (which are incorporated by reference herein):

US20040048802A1,	US20040043949A1,
US20040001853A1,	US20030008828A1,
US20020182227A1,	US20020177725A1,
US20020150947A1,	US20050267018A1,
US20020034732A1,	US20010034019A1,
US20050153877A1,	US20050074465A1,
US20050053921A1,	US20040253577A1,
US20040229936A1,	US20040229840A1,
US20040077551A1,	EP1408031A1, WO9837180A2, U.S.
Pat. No. 6,696,281B1, JP11137252A, WO0111089A1, U.S.	
Pat. No. 6,280,940B1, EP1106702A1, US20050118603A1,	
JP2000007645A, WO0053740A1, WO0020400A1,	

WO2002100900A2, WO0155703A1, US20030125541A1, US20040039187A1, U.S. Pat. No. 6,608,027B1, US20030224977A1, WO2003010141A2, WO2003007945A1, WO2002052015A2, WO0248375A2, WO0066623A2, WO0009543A2, WO9907734A2, U.S. Pat. No. 6,767,991B1, US20030187018A1, US20030186895A1, WO2004087741A1, WO2004039970A1, WO2004039833A1, WO2004037855A1, WO2004030670A1, US20040229818A1, US20040224900A1, WO2005028501A1, WO2004103996A1, WO2004065367A1, WO2004064925A1, WO2004093915A1, WO2004009121A1, WO2003066103A1, WO2005034850A2, WO2004094452A2, WO2004015131A2, WO2003099316A1, WO2003099274A1, WO2003053349A2, WO2002060926A2, WO040745A1, U.S. Pat. No. 6,586,615B1, WO2002061048A2, WO0248157A2, WO0248116A2, WO2005017125A2, WO0022160A1, US20060051745A1, WO2004021871A2, WO2004011647A1, WO9816657A1, U.S. Pat. No. 5,371,017A, WO9849190A2, U.S. Pat. No. 5,807,829A, WO0005243A2, WO0208251A2, WO2005067437A2, WO9918856A1, WO0004914A1, WO0212543A2, WO9845040A1, WO0140262A1, WO0102424A2, WO0196540A2, WO0164678A2, U.S. Pat. No. 5,512,391A, WO0218369A2, WO9846597A1, WO2005010029A1, WO2004113365A2, WO2004093798A2, WO2004072243A2, WO9822496A2, WO2004046159A1, JP11199509A, WO2005012288A1, WO2004108687A2, WO9740168A1, US20060110755A1, WO2002093519A2, U.S. Pat. No. 6,187,905B1, WO2003077729A2, WO9524414A1, WO2005009418A2, WO2004003000A2, US20050037018A1, WO9963998A1, WO0063444A2, WO9938888A2, WO9964442A1, WO0031129A1, WO0168818A2, WO9812308A1, WO9522985A1, WO0132691A1, WO9708304A2, WO2002079234A1, JP10298151A, JP09206076A, JP09009961A, JP2001103993A, JP11127861A, JP11124400A, JP11124398A, WO2003051910A2, WO2004021861A2, WO9800548A1, WO2004026896A2, WO0116379A1, U.S. Pat. No. 5,861,297A, WO2004007512A2, WO2004003138A2, WO2002057287A2, WO2004009020A2, WO2004000858A2, WO2003105770A2, WO0114517A1, WO9805333A1, U.S. Pat. No. 6,280,728B1, EP1443116A1, US20040063911A1, WO2003076466A1, WO2002087500A2, WO0190121A2, WO2004016222A2, WO9839030A1, WO9846630A1, WO0123331A1, WO9824766A1, U.S. Pat. No. 6,168,942B1, WO0188113A2, WO2005018330A1, WO2005003147A2, WO9115596A1, WO9719103A1, WO9708194A1, WO2002055693A2, WO2005030796A1, WO2005021584A2, WO2004113295A1, WO2004113294A1, WO2004113272A1, WO2003062228A1, WO0248172A2, WO0208198A2, WO0181325A2, WO0177113A2, WO0158929A1, WO9928482A2, WO9743310A1, WO9636702A2, WO9635806A1, WO9635717A2, U.S. Pat. No. 6,326,137B1, U.S. Pat. No. 6,251,583B1, U.S. Pat. No. 5,990,276A, U.S. Pat. No. 5,759,795A, U.S. Pat. No. 5,714,371A, U.S. Pat. No. 6,524,589B1, WO0208256A2, WO208187A1, WO2003062265A2, U.S. Pat. No. 7,012,066B2, JP07184648A, JP06315377A, WO2002100851A2,

JP11292840A, JP08205893A, WO0075338A2, WO0075337A1, WO2003059384A1, WO2002063035A2, WO2002070752A1, U.S. Pat. No. 6,190,920B1, WO2002068933A2, WO0122984A1, JP04320693A, JP2003064094A, WO179849A2, WO0006710A1, WO0001718A2, WO0238799A2, WO2005037860A2, WO2005035525A2, WO2005025517A2, WO2005007681A2, WO2003035060A1, WO2003006490A1, WO0174768A2, WO0107027A2, WO0024725A1, WO0012727A1, WO9950230A1, WO9909148A1, WO9817679A1, WO9811134A1, WO9634976A1, WO2003087092A2, WO2005028502A1, U.S. Pat. No. 5,837,464A, DE20201549U1, WO2003090674A2, WO9727334A1, WO0034308A2, U.S. Pat. No. 6,127,116A, US20030054000A1, JP2001019699A, U.S. Pat. No. 6,596,545B1, U.S. Pat. No. 6,329,209B1, IT1299179, CA2370400, KR2002007244, KR165708, KR2000074387, KR2000033010, KR2000033011, KR2001107178, KR2001107179, ES2143918, KR2002014283, KR149198, KR2001068676.

BRIEF DESCRIPTION OF THE FIGURES

[0039] FIG. 1 presents a cross-sectional schematic view of a Tee-fitting apparatus useful for combining solution and anti-solvent streams in accordance with the present invention.

[0040] FIG. 2 presents a schematic flow diagram of an apparatus which includes a mixing Tee for producing a precipitate in accordance with the present invention.

[0041] FIG. 3 presents a graphic representation of the effects of distillation on softening point of precipitate produced.

[0042] FIG. 4 presents a schematic diagram of a manufacturing process.

[0043] FIG. 5 presents a graphic representation of the softening point of comparative particulate materials prepared using a stirred batch process.

[0044] FIG. 6 presents a graphic representation of the effects on bioavailability of using SLS in a formulation compared with a similarly prepared formulation that does not employ SLS.

[0045] FIG. 7a presents an SEM 25× magnification photomicrograph showing granulate morphology before exposure to a temperature above its softening temperature.

[0046] FIG. 7b presents an SEM 25× magnification photomicrograph showing granulate morphology after exposure to a temperature above its softening temperature.

[0047] FIG. 8 presents a comparison of chord length in precipitated agglomerates as a function of the Reynolds numbers attained by the combining anti-solvent and solution streams.

[0048] FIG. 9 presents a correlation between processing stage and bulk surface area in precipitated and agglomerated materials.

[0049] FIG. 10 presents a comparison in C_{max} and AUC between 800 mg doses administered as a single dose and administered as multiple 200 mg doses over 3 hours (see Example V, infra, for details).

[0050] FIG. 11 presents the mean QTcF change from base-

prising 800 mg (LD) and 1200 mg (HD) doses of the compound of Formula B, moxifloxacin (MOX) and placebo (PBO) versus time.

DETAILED DESCRIPTION OF THE INVENTION

[0051] A method of making the compound of Formula B is described in U.S. Pat. No. 7,012,066 to Saskena, et al. (the '066 patent). In particular the '066 patent specifically describes the preparation of the compound of Formula B at col. 113, Example XXIV (cols. 448 to 451) and col. 1259. These sections in particular, and the entirety of the '066 patent are incorporated by reference herein. Improved processes for synthesizing the compound of Formula B are described in U.S. patent application Ser. No. 11/598,528, filed Nov. 13, 2006 (the '528 application) and International patent application no. 2006/048613 (the '613 application), filed Dec. 20, 2006. The '528 describes, on pages 10 through 13 and examples 1 to 2, improvements on the process described in the '066 patent for the preparation of the compound of Formula B, which pages, along with the entirety of the '528 application, are incorporated herein by reference. The '613 application describes, on pages 19 through 39, improvements in the improvements on the process described in the '066 patent for the preparation of the compound of Formula B, which pages, along with the entirety of the '613 application, are incorporated herein by reference.

[0052] The term "anti-solvent" as used herein is a liquid which reduces the solubility of a compound of interest when the anti-solvent is mixed into a solution comprising a solvent and the compound of interest. Accordingly, a sufficient quantity of an anti-solvent mixed with a solution comprising a compound of interest causes the compound of interest to come out of solution and precipitate as a particulate material.

[0053] The term "chord length" used herein refers to the length of a theoretical cord required to traverse one particle. Therefore, each particle has a chord length distribution characteristic of its size and shape.

[0054] As used herein "primary particle" is the initially formed particles nucleated by combining a solution and anti-solvent. "Primary particle size" refers to the size of a primary particle and is determined by Scanning Electron Microscopy (SEM).

[0055] As used herein, the term "precipitated particle" refers to a particle formed in a slurry by aggregation of primary particles. As used herein the term "agglomerated particulate" refers to an agglomeration of precipitated particles. As the terms are used herein "particle" and "particulate" pertains to material formed by precipitation processes and "granulate" refers to an agglomeration or aggregation of particles or an aggregation or agglomeration of a mixture of constituents, for example, a "granulate" prepared by agglomerating a powdered mixture of solids with a granulation fluid.

[0056] As used herein "median precipitated particle size" "median aggregate particle size" and "particulate size distribution" are determined by Laser Diffraction (LC) measurements.

[0057] As used herein, unless specified otherwise, the abbreviation "nm" means nanometers.

[0058] As used herein, the abbreviation "M" means molar unless specified otherwise

[0059] The term "Reynolds Number" (Re) as used herein is the conventional definition arising from fluid dynamics, a dimensionless parameter defined as:

[0060] wherein

[0061] ρ =fluid density

[0062] μ =viscosity coefficient

[0063] ν =kinematic viscosity

[0064] U=characteristic velocity

[0065] L=characteristic length scale

As is known, Reynolds Number reflects whether a fluid is flowing under a condition of laminar or turbulent flow. In general, laminar flow conditions exist at Reynolds numbers of less than about Re=2100. Above about Re=2100 the flow begins to become turbulent, and above about Re=10,000 the flow becomes chaotic.

[0066] When precipitating material to provide an active pharmaceutical ingredient (API) for inclusion in a medication it is necessary to tightly control the average primary particle size and the primary particle size range distribution, the average size (chord length) of agglomerates of primary particles (precipitated particles), and the size range distribution of the agglomerated particulate material (as these terms are defined above). It is also necessary to tightly control the bulk surface area and bulk density of the agglomerated particulate material, and the amount of solvent included in both primary and precipitated particles as well as the agglomerates particulate material. These parameters affect the physical properties of the particulate material produced, for example, softening point, bulk density and handling characteristics important to medicament formulation. Also affected are the pharmacological properties of the API, for example, dissolution rate, stability, and bioavailability, and the parameters employed in additional processing steps that the particulate may be subjected to in finishing the agglomerated particulate material, for example, the drying time and the maximum drying temperature which will be tolerated by the particulate material isolated from the precipitation slurry.

[0067] As discussed above, the solution/anti-solvent method for precipitation of the compound of Formula B requires the use of solutions having a high concentration of Formula B dissolved therein to minimize the anti-solvent volume used to precipitate the compound and to minimize the amount of unrecovered Formula B. When state of the art batch crystallizers are employed to carry out the precipitation of the compound of Formula B, large gradients in concentration of the solvent as it is mixed with the anti-solvent yield precipitated material having a large particle size range, and undesirably large average primary particle size and undesirably large average agglomerate particulate size. Moreover the precipitate product lacks batch to batch consistency both with regard to particulate average size and the amount of included solvent. In addition, it is inconvenient and inefficient to carry out batch operations for isolating and purifying the active compound on a commercial scale.

[0068] One aspect of the present invention is a process for precipitating an amorphous compound by a solution/anti-solvent technique, wherein the precipitate has a controlled narrow size range (microns) and a controlled narrow range in bulk surface area (m^2/g). Optionally, the present invention process further comprises subjecting the precipitated compound to controlled agglomeration by distilling off some of the supernatant liquid from the slurry initially prepared in the precipitation process (initial slurry) to provide a granulate material having a narrow size range and narrow range of bulk surface area. Each of these aspects of the process are discussed in turn.

[0069] The present invention provides, surprisingly, a precipitation process consistently yielding solids having a nar-

process comprises combining a stream of anti-solvent and a stream of a solution containing the compound to be precipitated, where the streams are combined with the solution stream perpendicular to the flow of the anti-solvent stream at an angle (measured relative to the direction of the anti-solvent stream flow) of substantially 90 degrees, and wherein the conditions for providing the anti-solvent stream are selected to give a Reynolds number of at least about 9000 and the conditions for providing the solution stream are selected to give a Reynolds number which is at least sufficient to produce turbulent flow, for example, an Re to about 2000. Preferably, the anti-solvent is supplied under conditions selected to provide an Re at least about 9,000, more preferably at least about 20,000 and the solution is supplied under conditions yielding a Reynolds number of Re at least about 5500.

[0070] Accordingly, the inventors have surprisingly found that an amorphous, solid form of the compound of Formula B having controlled primary particle size in the range of from about 200 nm to about 300 nm, with a bulk surface area of from about 25 m²/g to about 32 m²/g can be provided using the process of the present invention. Moreover, when the optional, subsequent agglomeration step (described below) is carried out the inventors have surprisingly found that the process of the present invention provides a particulate having desirable agglomerate chord length with a bulk surface area of from about 5 m²/g to about 8 m²/g, and a bulk density of from about 0.15 g/ml to about 0.19 g/ml.

[0071] With reference to FIG. 1, precipitation of the compound of Formula B in accordance with the process of the present invention can be carried out on a continuous basis by using a simple apparatus having a mixing chamber comprising a mixing Tee (1), and optionally connected to the outlet leg (2) of the Tee run, static mixer (3), wherein a stream of anti-solvent is passed through the straight run inlet (4) via anti-solvent inlet line (5) in the direction of Arrow (6), and a stream of a solution comprising the compound of Formula B is passed into the branch run (7) via solution inlet line (8) in the direction of arrow (9). In one example, Tee (1) is a standard 3/8" steel Tee fitted with a 1/2" inlet line (5), a 3/8" static mixer (3), and a 1/8" solution inlet line (8). Using this apparatus, the precipitation process of the invention is carried out by providing the solution stream to the apparatus at a rate yielding a Reynolds number of at least about 5,500 and providing an amount of the anti-solvent at a rate to achieve a Reynolds number of at least about 9,000. In some embodiments using an apparatus having such relative dimensions it is preferred to establish conditions to provide one stream, for example, the solution stream, yielding the desired Reynolds number and maintain a volumetric ratio of the volume of the anti-solvent to the volume of solution of from about 3:1 anti-solvent: solution to about 15:1 anti-solvent: solution. Preferably, the ratio of the volume of anti-solvent to solution is supplied to the mixing Tee at a ratio of about 4:1 anti-solvent: solution. Using the simple mixing apparatus described the inventors have found that conveniently these desired volumetric ratios are achieved when the solution is provided to the mixing Tee at a rate yielding a Reynolds number of at least about 5,500, preferably at least about 10,000, and the anti-solvent is provided to the mixing Tee at a rate yielding a Reynolds number of at least about 9,000, preferably at least about 15,000 and more preferably at least about 20,000. In some embodiments it is preferred to supply the anti-solvent under conditions yielding a Reynolds number of at least

[0072] Using the compound of Formula B, the inventors have surprisingly found that when the solution and anti-solvent are combined under the above-described conditions in a simple apparatus there is achieved sufficiently rapid mixing of the anti-solvent and solution in the Tee to provide consistently a particulate amorphous solid of the compound of Formula B which has a narrow primary particle size range, facilitating the provision of a granular agglomerate having desirable physical properties suitable for use as an active pharmaceutical ingredient (API) in the provision of a medicament.

[0073] Using as an example an apparatus having a mixing chamber constructed from a plumbing Tee fitting with a nominal outside diameter run of 3/8" (fitted with 1/2" inlet and outlet tubing) and a nominal outside diameter branch leg of 1/4" (fitted with 1/8" supply tubing), the desired flow conditions are realized by supplying an n-heptane anti-solvent flow rate of from about 3300 ml/min to about 4200 ml/min through the mixing Tee run, and a solution flow rate of from about 380 ml./min. to about 880 ml./min. through the mixing Tee branch leg, where the solution comprises MTBE and has dissolved therein from about 80 mg/ml to about 250 mg/ml of the compound of Formula B. It will be appreciated that other diameters and configurations of mixing chambers can be employed by varying the supply rate of the anti-solvent and solution to achieve the minimum desirable Reynolds number and provide the desired volumetric ratio of anti-solvent and solution.

[0074] Conveniently, a suitable mixing chamber for use in the process of the present invention can be provided by a standard, commercially available 90 degree Tee fitting, for example, a conventional plumbing Tee fitting, a compression Tee fitting, and a Swagelok™ Tee fitting. While a strict 90 degree relationship between anti-solvent and solution streams is not required, it is preferably to utilize a plumbing fitting which to a substantial degree does not supply the solution of the compound of Formula B to the anti-solvent stream with (from the anti-solvent frame of reference) any co-current component. To the degree that a fitting is used having inlets which impart some concurrent character, it will be appreciated that adjustments should be made to increase the Reynolds numbers of the combining anti-solvent and solution streams, providing a more turbulent mixing environment to compensate for the co-current component of the combination.

[0075] Thus, for example, if the mixing chamber had the configuration of a Y-fitting having input legs less than 120 degrees apart (thus they form an angle of greater than 120 degrees with the common leg), the two narrow angle legs could be utilized for solution and anti-solvent input with a selection of conditions leading to a concomitant increase in the Reynolds number of the inlet streams to offset the co-current component of the combining streams. Conversely, if such a Tee were used with the common leg and one narrow-angle leg employed as the inlet legs, and thus the streams are combined with an impinging component, a selection of conditions leading to a concomitant decrease in the Reynolds number of the input streams could be employed taking advantage of the degree to which the streams combined with an impinging component that improves the mixing of the combining streams. Accordingly, fittings having leg configurations other than a Tee-configuration may be employed in the process of the present invention with suitable alteration of

configurations having an orientation imparting a substantial co-current or impinging component to the combining streams.

[0076] Optionally a conventional static mixer can be employed on the outlet leg of the mixing chamber, for example a Model 1-TU-3L-12-1 static mixer from KoFlo Corporation (Cary, Ill.) providing additional control of the physical properties of the particulate produced by increasing the mixing time and intensity of the solution and anti-solvent after the streams are combined.

[0077] Different solvent and anti-solvent combinations may be employed depending upon the compound to be precipitated. For the compound of Formula B, preferably the anti-solvent is selected from the group consisting of linear or branched hydrocarbons having from about 5 carbon atoms to about 12 carbon atoms, preferably from about 5 carbon atoms to about 8 carbon atoms, more preferably linear hydrocarbons having from about 5 to about 8 carbon atoms, more preferably n-heptane. For the compound of Formula B, preferably the solvent used to provide a solution of the compound of Formula B is selected from acetone, methyl-tertiarybutyl-ether (MTBE), and mixtures of ethyl acetate and MTBE, more preferably the solvent is MTBE. When acetone is selected as a solvent it is preferred to use water as an antisolvent. When MTBE or mixtures of MTBE and ethyl acetate are selected as a solvent it is preferable to use n-heptane as an anti-solvent. In precipitating the compound of Formula B in accordance with the present invention method it is preferred to use MTBE as a solvent and n-heptane as an antisolvent.

[0078] In some embodiments when it is not desirable to carry out a subsequent optional step of distilling off supernatant liquid from the collected initially formed slurry (described herein), preferably the solution and anti-solvent are dried rigorously prior to combining the streams and forming the precipitate, thus substantially eliminating water from the initially formed slurry. Examples of drying methods which may be employed include filtration through a medium that absorbs water, for example, CUNO filtration, distillation methods, and contacting the solution or anti-solvent with a drying agent, for example, molecular sieves.

[0079] The precipitation process of the present invention is preferably run with a highly concentrated solution of the compound to be precipitated. In some embodiments it is preferred for the solution of the compound of Formula B to contain from about 80 g of the compound of Formula B/ml of solution (0.15 M) to about 250 mg of the compound of Formula B/ml of solution (0.48 M). In some embodiments it is preferred to use a solution comprising about 166 mg of the compound of Formula B/ml of solution (0.32 M). In some embodiments utilizing these concentrations it is preferred to maintain the solution at a temperature of from about -20°C . to about $+25^{\circ}\text{C}$., preferably at a temperature of from about -10°C . to about $+20^{\circ}\text{C}$., and more preferably the solution is maintained at 0°C . In some embodiments of the precipitation process of the invention, when the compound to be precipitated is the compound of Formula B, it is preferred to maintain both the anti-solvent and the solution of the compound of Formula B at a temperature of from about -25°C . to about $+25^{\circ}\text{C}$., preferably from about -25°C . to about $+20^{\circ}\text{C}$. In some embodiments it is preferred to use a solution comprising about 166 mg of the compound of Formula B/ml of solution (0.32 M) and to maintain the solution at a tempera-

[0080] The present invention precipitation process can be carried out in an apparatus that includes thermally controlled supply lines, mixing chamber (for example, a cooling line-traced mixing Tee) and conduits to maintain any desired temperature. In some embodiments it is preferred to maintain the supply lines and mixing chamber at ambient temperature, typically about 25°C ., and supply the mixing chamber with anti-solvent and solution of the compound of Formula B which has been maintained at a desired temperature, such that upon combining the streams the slurry produced is permitted to warm to the ambient temperature as it passes through the system. In some embodiments of the precipitation process the supply of solution and anti-solvent are preferably maintained at a temperature of from about -25°C . to about $+20^{\circ}\text{C}$. In some embodiments of the precipitation process it is preferred to maintain the supply of the solution of the compound of Formula B at a temperature of from about -10°C . to about 20°C .

[0081] In some embodiments it is preferred to trace the supply conduit for the solution of the compound of Formula B up to the mixing chamber with a cooling line, and thereby maintain the solution entering the mixing chamber at a temperature of about 0°C . In some embodiments it is preferred to trace the anti-solvent supply conduit up to the mixing chamber with a cooling line to maintain the anti-solvent supply at a temperature of about -20°C . When a solution of the compound of Formula B is supplied to the mixing chamber at 0°C . and the anti-solvent is supplied to the mixing chamber at -20°C . it is typically found that the slurry produced has a temperature of about -15°C .

[0082] The present invention process used to precipitate the compound of Formula B can be employed as part of a continuous precipitation process. For example with reference to FIG. 2, as shown schematically in FIG. 2, inlet run leg of mixing tee (1) can be supplied from storage tank (2), with anti-solvent and the branch leg inlet of mixing tee (1) can be supplied with a solution of the compound of Formula B from storage tank (3) through check valve (6). The combined solution and anti-solvent (which produces a slurry as the compound of Formula B precipitates) can be conducted from the mixing Tee (1) outlet, optionally through a static mixer (7), to holding tank (8). Accordingly in this manner the compound can be precipitated in the mixing Tee continuously. With further reference to FIG. 2, if the slurry formed in the mixing tee is conducted through a conduit having an output which can be directed to one of several to holding tanks (8), as each tank reaches capacity, the collected slurry can be further processed while the precipitation process carried out in the mixing tee continues to run with the outlet of the mixing tee conducted to a fresh holding tank. Alternatively the output of the mixing Tee and optional static mixer can be conducted directly to a device for separating the precipitate from the liquids, for example, a vacuum filtration device, a centrifuge, or a settling tank for decantation of the combined solvent and anti-solvent.

[0083] With reference to FIG. 2, when the mixing device is supplied by storage tank (2) of anti-solvent and storage tank (3) of a solution of the compound of Formula B, the flow of anti-solvent and solution through the mixing Tee can be controlled by any means, for example, control valves (4), selected, for example from a throttling valve, a needle valve, a metering pump, a flow meter, and a mass flow controller. It will be appreciated that other means for regulating the flow of

capsules using a Bosch capsule filler equipped with a 19 mm dosing disk, corresponding to 200 mg of active material/capsule.

[0438] Samples of these capsules were administered to healthy volunteers, either 4 capsules at once or spaced at 1 hour dosing intervals over a three hour period. The results are shown in FIG. 10, which indicates a C_{max} (single dose) at 3.1 hours of 2106 ng/ml and a C_{max} (multiple dose) at 4.25 hours of 1631 ng/ml. The corresponding single dose AUC was found to be 7029 ng·hr/ml and the corresponding multiple dose AUC was found to be 6410 ng·ml/hr, indicating that the formulation can provide therapeutic levels of the HCV protease inhibitor API contained therein.

Example V

Pharmaceutical Formulations

[0439] Additional batches of the granular pharmaceutical formulation were prepared using the process described in Example IV, albeit utilizing appropriate scale equipment for larger (250 Kg) and smaller (3 Kg) batch sizes, as indicated in the table below. With reference to the table below, the weights of the constituents used in each batch are reported (half of the croscarmellose sodium and microcrystalline cellulose reported is present in the product granular pharmaceutical formulation as intragranular material and half was blended with the granular material in the preparation of the formulation in accordance with the process described in Example IV, and therefore is extragranular material).

	Batch Size		
	3 kg	40 kg ^a	250 kg ^a
Constituents	kg/Batch	kg/Batch	kg/Batch
SCH 503034	1.5 (50 wt. %)	20 (50 wt. %)	125 (50 wt. %)
Lactose	0.27 (9 wt. %)	5.6 (14 wt. %)	35 (14 wt. %)
Monohydrate			
Microcrystalline	0.3 (10 wt. %) ^b	4 (10 wt. %) ^b	25 (10 wt. %) ^b
Cellulose			
Pregelatinized	0.45	6	37.5
Starch	(15 wt. %)	(15 wt. %)	(15 wt. %)
Croscarmellose	0.18	2.4	15
Sodium	(6 wt. %) ^b	(6 wt. %) ^b	(6 wt. %) ^b
Tartaric acid	0.15 (5 wt. %)	—	—
Sodium Lauryl	0.09	1.2	7.5
Sulfate	(3 wt. %)	(3 wt. %)	(3 wt. %)
Magnesium	0.06	0.8	5
Stearate	(2 wt. %)	(2 wt. %)	(2 wt. %)
Total Batch	3	40	250
Weight			
Process			
Equipment:			
Granulator	Low Shear Mixer	High Shear Granulator	High Shear Granulator
Dryer	Oven	Fluid Bed Dryer	Fluid Bed Dryer
Blender	Tumble Blender	Tumble Blender	Tumble Blender
Capsule	Encapsulator	Encapsulator	Encapsulator
Filling Machine	(Dosing disc)	(Dosing disc)	(Dosing disc)

^aTwo blends can be combined into one blend before encapsulation,
^bHalf is intragranular, half extragranular

Capsule Dissolution Characteristics

[0440] Aliquots of each of the granular pharmaceutical formulation prepared above were placed into capsules and tested for dissolution characteristics in accordance with the following process. The dissolution testing apparatus employed was a USP11 apparatus Paddle Stirrer filled with 900 mL of dissolution medium consisting of 0.5% sodium lauryl sulfate solution buffered with pH 6.8 sodium phosphate buffer. The dissolution tests were conducted at 37° C. The tests were carried out by stabilizing the dissolution medium at the test temperature with the paddles set at 50 RPM. Test capsules were dropped into the dissolution medium with the paddles actuated. Periodically aliquot samples of the dissolution media were withdrawn and analyzed by HPLC for active content. The total amount of active present in the dissolution media was calculated based on the HPLC determination and reported as a percentage of the total amount of active initially contained in the capsule dissolved into the dissolution media. The results for a representative sample taken from capsules prepared with each batch size are shown below in the table below as an average of 6 capsules.

Constituents	Source		
	3 kg Batch mg/cap	40 kg Batch mg/cap	250 kg Batch mg/cap
Precipitated Compound of Formula B	200	200	200
lactose Monohydrate	36	56	56
Microcrystalline Cellulose	40	40	40
Pregelatinized Starch	60	60	60
Croscarmellose Sodium	24	24	24
Sodium Lauryl Sulfate	12	12	12
Tartaric acid	20	—	—
Magnesium Stearate	8	8	8
Capsule Fill Weight	400	400	400
Dissolution Time:	% API	% API	% API
	Dissolved	Dissolved	Dissolved
10 minutes	65	78	83
20 minutes	84	88	92
30 minutes	92	91	94
45 minutes	98	95	96
60 minutes	100	98	97

Comparative PK Results-1

[0441] Capsules prepared using a formulation as described above for the 3 Kg batch and a formulation prepared by the same process, albeit on a laboratory scale and not employing sodium lauryl sulfate in the granulating fluid were administered to 12 healthy human volunteers. Accordingly, each of the test subjects received 2 capsules containing 200 mg of the API in a single administration. Blood samples were collected from each volunteer at predose (hour 0) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, and 24 hours post administration with the average concentration values for those subjects receiving the API presented graphically in FIG. 6 as the trace represented by the square datapoints. The serum drug levels of the volunteers receiving active drug are reported also in tabular form below, which table contains one column of results for

pharmacokinetic (PK) data from this study showed that for the dosage form prepared with sodium lauryl sulfate in the granulating fluid the mean maximum plasma concentration following a single administration (C_{max}) was on average 864 ng/ml, the median time (hours) to reach maximum concentration (T_{max}) was 1.71 hours, and the AUC 24 (areas under the plasma concentration time curve in ng·hr/mL for 24 hours post administration) was 2540.

Time from administration (hours)	Plasma Concentration (ng/ml)	
	0% SLS	3% SLS
0	0.0	0
0.5	9.34	386.1
1.0	86.9	671.1
1.5	183.9	701.8
2.0	220.0	525.8
2.5	211.5	484.2
3.0	208.3	400.1
4.0	137.9	263.9
5.0	173.3	145.5
6.0	127.4	88.6
7.0	99.8	57.7
8.0	77.0	45.1
9.0	49.0	35.9
10.0	52.8	32.4
12.0	34.3	19.7
24.0	10.4	6.15

[0442] With reference to FIG. 6, when compared to a formulation not containing sodium lauryl sulfate (trace with open circle datapoints), the present formulation shows improved bioavailability upon administration.

Comparative PK Results-2

[0443] A study was conducted to evaluate the effect of both a therapeutic (800 mg TID) and a supratherapeutic (1200 mg TID) dose of the compound of Formula B at steady-state on QT/QTc intervals, as measured by mean maximum change from time-matched baseline ECG recordings compared to placebo. The study was a multi-period, multiple-dose, placebo and active control study in healthy volunteers conducted in a randomized, evaluator blind, 4-way crossover manner. A formulation of the invention prepared as described above herein in Example IV (40 kg. batch scale) comprising the compound of Formula B, was administered in capsules.

[0444] Thirty-six subjects who met entry criteria received one of four study treatments for Days 1 to 5 of each treatment period. This study was conducted in a 4-way crossover manner so that subjects were randomized to receive the 4 study treatments in one of four sequences. Prior to treatment crossover, subjects completed an approximately 1-week outpatient washout period. Each treatment group consisted of oral dosing for 5 days of: A) a formulation of the invention comprising the compound of Formula B-800 mg TID; B) a formulation of the invention comprising the compound of Formula B-1200 mg TID; C) moxifloxacin-400 mg QD; and D) placebo.

API Source:

[0445] Treatment A:

[0446] A formulation of the invention comprising the compound of Formula B, 800 mg (4×200 mg Capsules)

[0447] Treatment B:

[0448] A formulation of the invention comprising the compound of Formula B, 1200 mg (6×200 mg Capsules) orally Q8^h for 4 days then as a single AM dose on Day 5

[0449] Pharmacokinetic samples for the determination of plasma concentrations of the compound of Formula B were collected on Day 5 of each period. PK samples were collected predose (0 hour), 1, 2, 3, 4, 6, 8, 12, and 24-hours postdose.

[0450] The following table shows the CV (coefficient of variance) around the mean of the compound of Formula B after multiple (Day 5) oral doses of a formulation of the invention comprising the compound of Formula B in healthy subjects.

Mean (CV) Pharmacokinetic Parameters		
Parameters	Mean (CV, %)	
	Formula B 800 mg (n = 31) ^{b,c}	Formula B 1200 mg (n = 35) ^c
T _{max} ^a (hr)	2.00 (1.00-4.00)	2.00 (1.00-4.00)
C _{max} (ng/mL)	1690 (19) ^d	1940 (24) ^e
C _{min} (ng/mL)	61.9 (41)	79.9 (46)
AUC(τ) (ng · hr/mL)	5320 (23) ^f	6500 (22) ^g
t _{1/2} (hr)	2.31 (68)	3.01 (73)
CL/F (L/hr)	158 (22)	196 (31)
Vd/F (L)	530 (84)	879 (85)

^aMedian (range)

^bThe four Subjects (101, 109, 160, and 166) were excluded from analysis of the Formula B 800 mg dose group as treatment at this dose was not completed

^cSubject 105 was excluded from the analysis of both Formula B treatment groups due to early withdrawal

^dIndividual C_{max} values ranged from about 1150 ng/ml to about 2500 ng/ml

^eIndividual C_{max} values ranged from about 1100 ng/ml to about 3150 ng/ml

^fIndividual AUC(τ) values ranged from about 3250 ng · hr/mL to about 8900 ng · hr/mL

^gIndividual AUC(τ) values ranged from about 2500 ng · hr/mL to about 9400 ng · hr/mL

Abbreviations used in the table:
AUC(τ) = area under the concentration-time curve during the dosing interval, C_{max} = maximum observed plasma concentration, C_{min} = minimum observed plasma concentration, CL/F = apparent total body clearance, t_{1/2} = terminal phase half-life, T_{max} = time of observed maximum concentration, Vd/F = apparent volume of distribution
The values for Formula B represent the calculated value from the sum of its diastereomers

[0451] FIG. 11 presents the mean QTcF change from a time-matched baseline. The figure shows that a formulation of the invention comprising compound of Formula B does not prolong the QT interval at either the 800 mg therapeutic dose (LD) or the 1200 mg supratherapeutic dose (HD) relative to the placebo. The moxifloxacin results, which show a lengthened QT/QTc interval, were included as a positive control.

Example VI

Pharmaceutical Formulations Using Other API

[0452] Using the above-described precipitation process, an API will be prepared for other compounds of the structure of Formula I (other than the compound of Formula B exemplified herein) and of the structure of Formulae II to XXVIII described herein. The precipitated particulate material will be incorporated into a pharmaceutical formulation by substituting it for the API in the process described above for preparation of granular pharmaceutical formulations in Examples IV

[0453] The above description of the invention is intended to be illustrative and not limiting. Various changes or modifications in the embodiments described herein may occur to those skilled in the art. These changes can be made without departing from the scope or spirit of the invention

1. A method of precipitating particles of a compound of Formula A having a size range of from about 200 nm to about 300 nm, the method comprising introducing a stream of a solution of the compound of Formula A into a stream of an anti-solvent for the compound of Formula A, wherein the anti-solvent stream is supplied under conditions yielding a Reynolds number of at least about 9,000, and the solution is supplied under conditions yielding a Reynolds number of at least about 2,000, and wherein the streams are introduced substantially absent any concurrent or impinging component.

2. The method of claim 1 wherein the anti-solvent is supplied under conditions yielding a Reynolds number of from about 9,000 to about 25,000.

3. The method of claim 2 wherein the solution containing the compound of Formula A is supplied under conditions yielding a Reynolds number of at least about 10,000.

4. The method of claim 3, wherein the compound of Formula A is 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide (the compound of Formula B), and the anti-solvent is supplied under conditions yielding a Reynolds number of at least about 23,000.

5. The method of claim 1 wherein the compound of Formula A is 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide (the compound of Formula B), the solution containing the compound of Formula B is supplied under conditions yielding a Reynolds number of 5,500 or more, and the volumetric ratio of the stream of solution of Formula B to the stream of anti-solvent is maintained at a ratio of from about 1:15 solution:anti-solvent to about 1:3 solution:anti-solvent.

6. The method of claim 5 wherein the ratio of the combined streams is maintained at about 1:4 solution:anti-solvent.

7. The method of claim 4 wherein the solution of the compound of Formula B comprises methyl-tertiarybutyl-ether (MTBE) solvent having from about 80 mg/ml of the compound of Formula B to about 250 mg/ml of the compound of Formula B dissolved therein and the anti-solvent is selected from linear or branched alkanes having from about 5 to about 12 carbon atoms.

8. The method of claim 7 wherein the anti-solvent is heptane.

9. The method of claim 8 wherein the solution contains an amount of the compound of Formula B of from about 80 mg/ml to about 200 mg/ml.

10. The method of claim 8 wherein the solution and anti-solvent are maintained and combined at a temperature of from about -20° C. to about +25° C.

11. The method of claim 10 wherein up to the point of mixing the solution is maintained at a temperature of about 0° C. and the anti-solvent is maintained at a temperature of about -20° C.

12. The method of claim 11 wherein the solution comprises about 166 mg/ml of the compound of Formula B.

13. The method of claim 3 wherein a solution concentration, a temperature of the solution and anti-solvent upon being introduced, and the conditions yielding Reynolds numbers for the solution and anti-solvent are selected to provide precipitated particles having a primary particle size of less

from about 1 micron to about 2.5 microns, a precipitated particle size distribution of from about 1 micron to about 50 microns, a bulk surface area of from about 25 m²/g to about 32.5 m²/g, and a softening point of from about 20° C. to about 50° C.

14. A method of providing an agglomerated particulate comprising collecting the precipitated particles provided by the method of claim 12 together with the solvent and anti-solvent and distilling off at least about 60 vol % of the combined liquids at sub-atmospheric pressure and a temperature below the softening point of the precipitated particles.

15. The method of claim 14 wherein the distillation conditions are selected to yield an agglomerated particulate having a median bulk surface area of from about 5 m²/g to about 12 m²/g, an agglomerated particulate median particle size of from about 1 micron to about 2.5 microns, an agglomerated particulate particle size distribution of from about 1 micron to about 50 microns and a softening point of from about 20° C. to about 50° C.

16. A process comprising combining a 0° C. stream of a solution comprising methyltertiarybutyl ether (MTBE) having dissolved therein 166 mg/ml of the compound of 3-[2-(3-tert-Butyl-ureido)-3,3-dimethyl-butyl]-6,6-dimethyl-3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid (2-carbamoyl-1-cyclobutylmethyl-2-oxo-ethyl)-amide (the compound of Formula B), with a -20° C. stream of heptane wherein the solution stream is provided under conditions yielding a Reynolds number of 10650, the heptane stream is supplied under conditions yielding a Reynolds number of 23,650 and the solution stream is combined at substantially a 90 degree angle to the anti-solvent stream, thereby providing a slurry comprising precipitated particles of the compound of Formula B.

17. The process of claim 16 further comprising the steps of collecting said slurry and distilling supernatant liquid from the collected slurry at subatmospheric pressure and at a temperature that forms an agglomerated particulate having a softening point of greater than about 25° C.

18. A process for making a classified granulate comprising:

(a) providing a dry-blended mixture by blending a sufficient amount of the precipitated particulate material (API) prepared in accordance with the process of claim 17 to provide 55.6 wt % of the granulate, an amount of microcrystalline cellulose sufficient to provide 5.6 wt. % of the granulate, an amount of pregelatinized starch sufficient to provide 16.6 wt. % of the granulate, an amount of croscarmellose sodium sufficient to provide 3.3 wt % of the granulate, and an amount of lactose monohydrate sufficient to provide 15.6 wt. % of the granulate;

(b) agglomerating the dry-blended mixture from step "a" using a granulating fluid comprising an amount of sodium lauryl sulfate sufficient to provide up to 6.6 wt. % of the granulate dissolved in a weight of water equal to from about 12 times to about 13 times the weight of sodium lauryl sulfate employed thereby providing a first granulate;

(c) wet-milling the first granulate from step "b" to provide a uniformly sized second granulate;

(d) drying the second granulate prepared in step (c) until the granulate displays a loss on drying (LOD) of from about 1.5 wt. % to about 2.5 wt. %; and

(e) dry-milling the dried second granulate through a screen.

19. The process of claim 18 wherein the amount of sodium lauryl sulfate used in granulating step "b" is an amount sufficient to provide the granulate 3.3 wt. % sodium lauryl sul-

20. The process of claim 18 wherein wet-milling step “c” is carried out in a wet mill equipped with a screen having 0.375 inch holes.
21. The process of claim 20 wherein drying step “d” is carried out in a fluid bed dryer.
22. The process of claim 21 wherein dry-milling step “e” is carried out in a screen mill equipped with a screen having 0.040 inch holes.
23. A process for providing a granular pharmaceutical formulation comprising the steps:
- (a) dry-blending the classified granulate from step “e” of claim 19 with an amount of microcrystalline cellulose equal to the amount of microcrystalline cellulose present in the classified granulate and an amount of croscarmellose sodium equal to the weight of the croscarmellose sodium present in the classified granulate to provide a homogeneous granular powder; and
 - (b) dry-blending the homogeneous granular powder from step “a” with an amount of magnesium stearate sufficient to provide 2 wt. % of the dry-blended product, thereby providing a granular pharmaceutical formulation.
24. A dosage form comprising an amount of the granular pharmaceutical formulation of claim 23 in a capsule.
25. The dosage form of claim 24 which on average exhibits the following dissolution profile when tested using a USP11 dissolution testing apparatus Paddle Stirrer filled with 900 mL of dissolution medium consisting of 0.5% sodium lauryl sulfate solution buffered with pH 6.8 sodium phosphate buffer at 37° C. and with the paddles set at 50 RPM:
- | Post DropTime: | % API Dissolved |
|----------------|-----------------|
| 10 minutes | 80 |
| 20 minutes | 90 |
| 30 minutes | 93 |
| 45 minutes | 96 |
| 60 minutes | 98 |
26. A dosage form comprising an amount of the granular pharmaceutical formulation of claim 24 containing 800 mg of the API which exhibits a Cmax of 2106 ng/ml at about 3.0 hours and an AUC of 7029 ng·hr/ml when administered as a single dose.
27. Precipitated particles prepared in accordance with the process of claim 13.
28. An agglomerated particulate prepared in accordance with the process of claim 14.
29. Precipitated particles prepared in accordance with the process of claim 4.
30. A classified granulate prepared in accordance with the process of claim 22.
31. A granular pharmaceutical formulation prepared in accordance with the process of claim 23.
32. A classified granulate prepared in accordance with the process of claim 18 wherein the compound of Formula A is substituted by a compound of any of the structures of Formula I to Formula XXVIII.
33. Precipitated particles comprising the compound of Formula B, having a primary particle size of less than about 1.0 micron, a precipitated particle size distribution of from about 1 micron to about 50 microns, a bulk surface area of from about 25 m²/g to about 32.5 m²/g, and a softening point of from about 20° C. to about 50° C.
34. An agglomerated particulate comprising the compound of Formula B having a median bulk surface area of from about

- 5 m²/g to about 12 m²/g, an agglomerated particulate particle size of from about 1 micron to about 2.5 microns, an agglomerated particulate particle size distribution of from about 1 micron to about 50 microns and a softening point of from about 20° C. to about 50° C.
35. A granulate comprising 55.6 wt. % of API, 5.6 wt. % microcrystalline cellulose, 16.6 wt. % pregelatinized starch, 3.3 wt. % croscarmellose sodium, 15.6 wt. % lactose monohydrate, and up to 6.6 wt. % sodium lauryl sulfate, the granulate having by a bulk density of from about 0.4 g/ml to about 0.6 g/ml, wherein said API is an agglomerated particulate comprising the compound of Formula B having a median bulk surface area of from about 5 m²/g to about 12 m²/g, an agglomerated particulate particle size of from about 1 micron to about 2.5 microns, an agglomerated particulate particle size distribution of from about 1 micron to about 50 microns, a bulk density of from about 0.15 g/ml to about 0.19 g/ml and a softening point of from about 20° C. to about 50° C.
36. The granulate of claim 35 wherein the sodium lauryl sulfate is present in an amount providing 3.3 wt. % of the granulate.
37. A granular pharmaceutical formulation comprising 50 wt. % API, 14 wt. % lactose monohydrate (intragranular), 5 wt. % intragranular microcrystalline cellulose, 5 wt. % extragranular microcrystalline cellulose, 3 wt. % intragranular croscarmellose sodium, 3 wt. % extragranular croscarmellose sodium, 15 wt. % pregelatinized starch (intragranular), 3 wt. % sodium lauryl sulfate (intragranular), and 2 wt. % magnesium stearate (extragranular), wherein said API is an agglomerated particulate comprising the compound of Formula B having a median bulk surface area of from about 5 m²/g to about 12 m²/g, an agglomerated particulate particle size of from about 1 micron to about 2.5 microns, an agglomerated particulate particle size distribution of from about 1 micron to about 50 microns, a bulk density of from about 0.15 g/ml to about 0.19 g/ml and a softening point of from about 20° C. to about 50° C.
38. A capsule comprising the granular pharmaceutical formulation of claim 37, having on average the following dissolution profile when tested using a USP11 dissolution testing apparatus Paddle Stirrer filled with 900 mL of dissolution medium consisting of 0.5% sodium lauryl sulfate solution buffered with pH 6.8 sodium phosphate buffer at 37° C. and with the paddles set at 50 RPM:
- | Post DropTime: | % API Dissolved |
|----------------|-----------------|
| 10 minutes | 80 |
| 20 minutes | 90 |
| 30 minutes | 93 |
| 45 minutes | 96 |
| 60 minutes | 98 |
39. A dosage form comprising an amount of the granular pharmaceutical formulation of claim 37 containing 800 mg of API which dosage form provides a Cmax of 2106 ng/ml at about 3.0 hours and an AUC of 7029 ng·hr/ml when administered to a human.
40. A dosage form comprising an amount of the granular pharmaceutical formulation of claim 37 containing 800 mg of API which dosage form does not prolong the QT interval relative to a placebo when administered to a human.

* * * * *



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. 11 160.575, titulada "PRODUCCIÓN DE MONOPARTÍCULAS ENCAPSULADAS EN FRACCIONES DE ALTO VOLUMEN", cuyo titular es **ICEUTICA PTY LTD.** publicada en la gaceta No. 647 del 29 de junio de 2012.

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 3 días del mes de Septiembre de 2012.

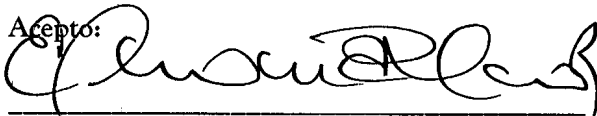

PROCAPS S.A.

C.C. N° 16'251.923
NIT: 890.106.527-5
Representante Legal

APROBADO

03 SET. 2012

PROCAPS S.A.

Acepto: 

ELIANA ISAURA MORENO BOHÓRQUEZ
C.C. 51.975.664
T.P. 83823 del C.S.J



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04*****

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

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

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 "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

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

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

PROCAPS S.A.

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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 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
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

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.

SIGLA: PROCAPS.

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 890.106.527-5.

MATRICULA MERCANTIL: 24,802.

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



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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

Dirección Comercial:

CL 80 No 78 B - 201 en Barranquilla.

Dirección Electrónica:

jcelis@procaps.com.co

Telefono: 3719278.

Dirección Judicial:

CL 80 No 78 B - 201 en Barranquilla.

Dirección Electrónica:

jcelis@procaps.com.co

Telefono: 3719278.

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 18 de Agosto de 2073.

C E R T I F I C A

OBJETO SOCIAL: El objeto principal de la sociedad sera: a) La fabricacion, importacion y comercializacion de alimentos procesados y suplementos dietarios. b) La fabricacion de capsulas 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 quimicas, farmaceuticas, alimenticias y cosmeticas, para uso y consumo humano y veterinario. c) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas, alimenticias y cosmeticas 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 fabricacion de sustancias quimicas, farmaceuticas, alimenticias y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. e) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. f) La compra, venta, exportacion, fabricacion, importacion, distribucion de dulces, confites, galletas y todo tipo de golosinas o alimentos para el consumo humano. g) Actuar como representante o agente de personas naturales y juridicas, nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualquiera de las actividades descritas en los literales a), b), c), d) y e) antes descritos. h) Prestar los

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servicios de asesorias y consultoria en las areas administrativas, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion, exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de PROCAPS S.A., asi como los de publicidad y promocion de productos quimicos, alimenticios, cosmeticos y farmaceuticos para uso humano, animal o industrial. i) Adquirir, operar, administrar y explotar, a cualquier titulo, empresa o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, alimenticios, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes 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 prestamo, 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 todo tipo de titulos valores e instrumentos negociables, comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles, designar representantes apoderados en el pais 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 podra garantizar el cumplimiento de sus obligaciones adquiridas por terceros o por sus socios, para lo cual podra inclusive constituir gravámenes reales sobre sus bienes de cualquier naturaleza.

C E R T I F I C A

CAPITAL	Nro Acciones	Valor Acci3n
Autorizado		
\$*****2,000,000,000	*****2,000,000	*****1,000
Suscrito		
\$*****1,298,000,000	*****1,298,000	*****1,000
Pagado		
\$*****1,298,000,000	*****1,298,000	*****1,000

C E R T I F I C A

ADMINISTRACION: La direccion y administracion de la sociedad correspondera a la Asamblea General de Accionistas, a la Junta Directiva, al Presidente, al Vicepresidente y a un Gerente General. Corresponde a la Junta Directiva las siguientes funciones y atribuciones entre otras: Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion. Cuando se trate de operaciones en virtud de las cuales la sociedad garantice obligaciones de terceros o de los socios, se requerira que la operacion sea aprobada con el voto de

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por lo menos 2/3 partes de los integrantes de la Junta Directiva. La sociedad tendra un Presidente , quien ejercera la representacion legal de la sociedad y tendra las siguientes atribuciones entre otras: Ejecutar las decisiones de la Asamblea General de Accionistas y de la Junta Directiva. Ejercer la Representacion 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, disistir y allanar a la sociedad en cualquier asunto judicial. Aprobar y celebrar en nombre de la socieda todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos colombianos a doscientos cincuenta mil dolares de los Estados Unidos de America (US\$250.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la transacion o celebracion del acto. Las demas funciones que le correspondan como Representante Legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Presidente tendra un suplente, designado por la Junta Directiva, quien reemplazara al Presidente en sus faltas temporales, absolutas o meramente accidentales, con entidades facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un Vicepresidente designado por la Junta Directiva, quien tambien ejercera la representacion legal de la sociedad, pudiendo ejercerla conjunta o separadamente con el Presidente. El vicepresidente tendra las siguientes facultades entre otras. Ejecutar dentro de su competencia las decisiones de la Asamblea General de Accionistas, de la Junta Directiva y del Presidente. Ejercer la representacion 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 cuantia sea igual o inferior al equivalente en pesos colombianos a ciento cincuenta mil dolares de los Estados Unidos de America (US\$150.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza muebles, acciones, cuotas o partes de interes 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

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

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cabeza del Presidente. Las demas funciones que le corresponda como Representante legal por disposicion de la ley, de estos estatutos o de la Junta Directiva. El Vicepresidente tendrá (1) suplente, designado por la Junta Directiva, quien lo reemplazara conjunta o separadamente en sus faltas temporales, absolutas o meramente accidentales, con identicas facultades y sin que sea necesario para ello acreditar la ausencia del principal. La sociedad tendra un (1) Gerente General, con su respectivo Suplente, designados por la Junta Directiva. El Suplente reemplazara al Gerente General, en sus faltas temporales, absolutas o meramente accidentales, quien junto con el gerente general, llevaran la representacion legal de la sociedad, con identicas facultades, pudiendolas ejercer conjunta o separadamente con el Presidente y Vicepresidente, con identicas facultades que el Gerente General y sin que sea necesario para ello acreditar la ausencia del titular. El Gerente General tendra las siguientes facultades entre otras: Ejercer la representacion 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. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a Cincuenta Mil dolares de los Estados Unidos de America (US\$50.000), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto, siempre que no se trate de enajenar a cualquier titulo bienes inmuebles o cualquier otro activo fijo de la sociedad, inclusive de naturaleza mueble, acciones, cuotas o partes de interes, inversiones y todo tipo de derechos de la sociedad o de constituir gravámenes sobre cualquiera de las anteriores facultades que radican exclusiva y privativamente en cabeza del Presidente.

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, y según Acta No. 127 del 22 de Marzo de 2000 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 29 de Mayo de 2000 bajo el No. 87,250 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

1. Minski Gontovnik Ruben	CC.*****7,463,982
2. Minski Gontovnik Meyer	CC.*****7,461,324
3. Minski Gontovnik Jose	CC.*****8,671,834

Suplentes

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

~~Barranquilla, 02 de Agosto de 2012 Hr:10:21:57~~

***** 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.

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
Organo 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 continuación: 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 ----
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 transaccion. Grupo A. WALTER NAKA

***** 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.

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 representacion 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 tambien los demas 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 representacion de -----
PROCANPS S.A., suscriban las declaraciones, reportes y cualquier
documento relacionado con los tramites 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 -----
representacion de PROCAPS S.A.; endosen los titulos valores de la
sociedad hasta por la suma de UN MIL MILLONES DE PESOS -----
(1.000.000.000.00) M.L. CUARTO: EI 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 Notaria 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 condicion de Presidente y Representante Legal de la
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 -----

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

Procesado por: [illegible] 07/02/2012

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

PROCAPS S.A.

NIT: 890.106.527-5.

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 MINSKI 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 Nacional de Estupefacientes e ICA, con el fin que gestione, tramite o presente las diferentes solicitudes y -----
peticiones de la empresa, según 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, según 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 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

***** 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.

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 D O

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 -----
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 -----

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 4,814 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 ó 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 4,815 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

***** 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.

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
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: -----

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

Form. Lit. - Barranquilla, 02 de Ago. - 8:50:10 am - Modificado en 07/02/2012

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

PROCAPS S.A.

NIT: 890.106.527-5.

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 Despecial, 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

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

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



***** Pag. 8
 C A M A R A D E C O M E R C I O
 D E B A R R A N Q U I L L A
 04*****

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

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

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 determinó: -----

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 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

***** 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.

Que su última Renovación fue el: 22 de Marzo de 2012.

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.

m. Rojas

