



No. 11-163902- -00004-0000

Fecha: 2012-09-12 16:23:45 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 34

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: 11 163.902

Solicitante: AMARIN PHARMA, INC

Apoderado: LUZ CLEMENCIA DE PAEZ

Título de la Nueva Creación: COMPOSICIÓN FARMACÉUTICA ESTABLE Y MÉTODOS PARA UTILIZAR LA MISMA

Gaceta: 647

2. Datos del Opositor

☐ Persona Natural ☒ Persona Jurídica
SYNTHESIS S.A.S.

Nombre o denominación /Razón social completa

LUIS PALACIOS ARAGON

Nombre del representante legal

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

Número 860000760-1 _____

Dirección. CRA 44 20C 73 _____ Ciudad BOGOTA

Teléfono 3692222 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

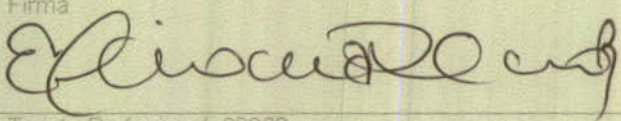
Causal: Art14, 16, 18,20 y 30 de la decisión 486 de la CAN no cumple con los requisitos De patentabilidad.

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 9 folios (obligatorios indicar cuántos).
- ☒ Anexo de fundamentos de la oposición. Se anexan 14 folios (obligatorios indicar cuántos)
- ☒ Copias para traslado.
- ☐ Copia de la solicitud y sus anexos en formato magnético.

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

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

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 12 - 0085323
		Bogotá D.C., Agosto 21 de 2012 - 14:34:18

RECIBIDO DE : LABORATORIOS SYNTHESIS S.A.S.					NI 860.000.760
*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	497473885	16/08/2012	1.575.000.00

*** Conceptos Pagados ***					
CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO	
1	50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	1632	OPOSICION NUEVA CRACION / PRESENTACION	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

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Act. 400 OPOSIOBSERVTER Folios: 34

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

Referencia : Expediente N° 11 163902
Asunto : Oposición a la solicitud de patente de Invención titulada
"COMPOSICIÓN FARMACÉUTICA ESTABLE Y
MÉTODOS PARA UTILIZAR LA MISMA"
Solicitante : AMARIN PHARMA, INC.
Opositora : LABORATORIOS SYNTHESIS S.A.S.

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 **LABORATORIOS SYNTHESIS S.A.S.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Bogotá, 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 "**COMPOSICIÓN FARMACÉUTICA ESTABLE Y MÉTODOS PARA UTILIZAR LA MISMA**", cuyo titular es **AMARIN PHARMA, INC.**, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

1. INTERÉS PARA ACTUAR

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular **ACIDOS GRASOS POLIINSATURADOS**. 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 29 de noviembre de 2011, reivindicando prioridad bajo la solicitud US20090173763 del 2009-04-29; 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 WO2010127103 del 2010-11-04.

2.2. La solicitud colombiana 11 163902 objeto de la presente oposición, se refiere a una composición farmacéutica que comprende por lo menos 95% de EPA encerrado en una cubierta de cápsula, en donde la composición tiene un valor inicial de peróxido no mayor de 5 Meq/kg y después de almacenamiento de la composición a 25° C y 60% de HR durante un periodo de 6 meses, la composición tiene un segundo valor de peróxido no mayor de 8 Meq/kg. Se refiere también a un método para tratar o prevenir una enfermedad cardiovascular en un sujeto en necesidad del mismo que comprende administrar al sujeto una cantidad terapéuticamente efectiva de la composición farmacéutica antes descrita.

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 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

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Bogotá Colombia

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: US2006134178 publicada el 22 de junio de 2006.
- D2: US2003104048 publicada el 05 de junio de 2003.

2.5. Por su parte, el documento D1, revela que a una sustancia orgánica que tiene un doble enlace tal como un ácido graso poliinsaturado se añadió un componente antioxidante que contiene un componente antioxidante de sésamo y ácido ascórbico o un éster de ácido graso de ascorbilo, y menciona que el método anterior proporciona una composición que contiene una sustancia orgánica que tiene un doble enlace exhibiendo una estabilidad oxidativa mejorada. En particular, según dicho documento D1, se mejora extremadamente la estabilidad oxidativa de la grasa y del aceite que contiene el ácido graso poliinsaturado. De manera particular, el mismo documento D1 describe una composición farmacéutica que comprende al menos 95% de EPA encerrada en una cápsula, en la que la composición tiene una línea base de peróxido no superior a 5 meq / kg.

2.6. El documento D2 describe por su parte, una cubierta de cápsula para encerrar los ácidos grasos esenciales, tales como EPA, que tiene 44% de material formador de película, 7% de glicerina, 18% de sorbitol, maltitol 6%, y 25% de agua, 35% de gelatina + 9% de goma de acacia = 44% material formador de película, como se puede ver de forma particular en los párrafos 0024 a 0034 que es idéntica a la Composición de Ensayo de la solicitud objeto de la presente oposición.

2.7. Como tal, la composición de la combinación del documento D1 con el documento D2, tendría inherentemente la estabilidad de almacenamiento sobre la cual se busca protección en el capítulo reivindicatorio de la solicitud colombiana objeto de la presente oposición. Así las cosas la solicitud colombiana 11 163902 carece evidentemente de Altura Inventiva

2.8. Por lo tanto, este documento objeto de oposición a la luz del documento D1, en combinación con el documento D2 carece evidentemente de ALTURA INVENTIVA y con base en el artículo 14 de la Decisión 486 de la CAN, carece de APLICACIÓN INDUSTRIAL.

2.9. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 11 163902 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con dos de los tres requisitos necesarios para su protección.

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

2.10.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *“Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”*. A la fecha de prioridad, 29 de abril de 2009, a partir del documento D1, en combinación con el documento D2, un

experto en la materia puede llegar de manera evidente a una composición farmacéutica que comprende por lo menos 95% de EPA encerrado en una cubierta de cápsula, en donde la composición tiene un valor inicial de peróxido no mayor de 5 Meq/kg y después de almacenamiento de la composición a 25° C y 60% de HR durante un periodo de 6 meses, la composición tiene un segundo valor de peróxido no mayor de 8 Meq/kg; sobre el cual busca protección en el capítulo reivindicatorio.

2.10.2. CARENCIA DE APLICACIÓN INDUSTRIAL La Decisión 486 de la CAN consagra en su artículo 14 lo siguiente: *“Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial”*. La presente solicitud carece de aplicación Industrial ya que como se demostró anteriormente, algunas cláusulas reclaman 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 terapéuticos, no cumple con el requisito de la aplicación industrial.

2.11. 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*



Derecho de la Competencia, Propiedad Industrial y Comercio Exterior

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

2.12. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada *“COMPOSICIÓN FARMACÉUTICA ESTABLE Y MÉTODOS PARA UTILIZAR LA MISMA”*, cuyo titular es AMARIN PHARMA, INC, 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: US2006134178 publicada el 22 de junio de 2006.
- D2: US2003104048 publicada el 05 de junio de 2003.

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Bogotá Colombia

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 **LABORATORIOS SYNTHESIS S.A.S.**
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: US2006134178 publicada el 22 de junio de 2006.
 - D2: US2003104048 publicada el 05 de junio de 2003.



Derecho de la Competencia, Propiedad
Industrial y Comercio Exterior

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 director,

ELIANA ISAURA MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

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

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Bogotá Colombia

ANEXO 1



US 20060134178A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2006/0134178 A1**
Doisaki et al. (43) **Pub. Date: Jun. 22, 2006**

(54) **COMPOSITION CONTAINING ORGANIC
SUBSTANCE HAVING DOUBLE BOND WITH
IMPROVED OXIDATIVE STABILITY**

(30) **Foreign Application Priority Data**

Nov. 22, 2002 (JP) 2002-339906

(76) **Inventors: Nobushige Doisaki, Tokyo (JP);
Tsuyoshi Koriyama, Tokyo (JP); Jun
Okano, Tokyo (JP); Shuji Jinno, Tokyo
(JP)**

Publication Classification

(51) **Int. Cl.**

A61K 47/00 (2006.01)

A61K 35/60 (2006.01)

(52) **U.S. Cl. 424/439; 424/523**

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WASHINGTON, DC 20036 (US)

(57)

ABSTRACT

To an organic substance having a double bond such as a polyunsaturated fatty acid was added an antioxidative component containing an antioxidative sesame component and ascorbic acid or an ascorbyl fatty acid ester. The above method provides a composition containing an organic substance having a double bond exhibiting enhanced oxidative stability. Particularly, it extremely improves oxidative stability of fat and oil which contains polyunsaturated fatty acid. General-purpose refined fish oil which is easy to handle can be provided for food, medicine or feed uses.

(21) **Appl. No.: 10/535,413**

(22) **PCT Filed: Nov. 21, 2003**

(86) **PCT No.: PCT/JP03/14877**

COMPOSITION CONTAINING ORGANIC SUBSTANCE HAVING DOUBLE BOND WITH IMPROVED OXIDATIVE STABILITY

TECHNICAL FIELD

[0001] The present invention relates to a composition containing an organic substance having a double bond with improved oxidative stability. More specifically, the present invention relates to a composition with improved oxidative stability that is prepared by adding an antioxidative sesame component and ascorbic acid or an ascorbyl fatty acid ester as antioxidants to an easily oxidizable organic substance having a double bond, such as a polyunsaturated fatty acid.

[0002] In the present invention, the polyunsaturated fatty acid refers to a fatty acid having at least three double bonds.

BACKGROUND ART

[0003] It has recently become known that oils and fats, particularly those containing polyunsaturated fatty acids, have physiologic activity. Accordingly, such oils and fats have been increasingly and widely used in food and animal feed as additives, from the viewpoint of health. Eicosapentaenoic acid and docosahexaenoic acid are polyunsaturated fatty acids mainly contained in fish oil. It has been found that they have the effect of, for example, preventing hyperlipemia, high blood pressure, skin aging, and the like, and they have been used in medical drugs and food with health-promoting benefits. Unfortunately, oils and fats containing such a polyunsaturated fatty acid have low oxidative stability. Accordingly, food to which such an oil or fat can be added is limited, or if added to food or the like, the oil or fat undesirably generates an odor due to its oxidation, even slight oxidation. How the oil or fat is handled needs to be taken into account. For example, refined fish oil remaining after use must be hermetically sealed with the can of the fish oil filled with nitrogen gas. Thus, there are limits in use, such as of product type, distribution temperature, content, and storage conditions.

[0004] Since, for example, docosahexaenoic acid and eicosapentaenoic acid play an important role to develop the brain and retinas and the memory and learning function of babies and breast milk contains these fatty acids, modified milk for babies to which fish oil containing docosahexaenoic acid and eicosapentaenoic acid has been added is commercially available. Also, since arachidonic acid plays an important role for growth and is contained in breast milk, addition of arachidonic acid to the modified baby milk has been attempted. However, it is necessary to take care not to oxidize polyunsaturated fatty acids when these polyunsaturated fatty acids are blended into the modified baby milk. Otherwise, oxidized odor is generated by oxidation, so that not only the modified milk becomes difficult to ingest, but also the modified milk itself may be degraded to be toxic.

[0005] Encapsulated eicosapentaenoic acid ethyl esters are commercially available as medical drugs for oral administration. Refined fish oil containing eicosapentaenoic acid and docosahexaenoic acid is also available in form of capsule as health food. Since these fatty acids are liable to be oxidized, their use is limited, except for use in capsules.

[0006] In order to enhance the oxidative stability, the oils and

encapsulated into microcapsules to be powdered, or enclosed with cyclodextrin and powdered so that stable powdered oil or fat is provided. However, this approach makes the production steps complicated and decreases productivity. In addition, capsules may be broken during storage, and the type of capsule applicable for food and animal feed is limited, disadvantageously.

[0007] In order to enhance the oxidative stability of oils and fats, various types of antioxidant have been used. For example, plural types of antioxidant are used in combination, or a synergist, such as phosphoric acid, citric acid, or ascorbic acid, is added to an antioxidant to enhance the antioxidant properties. However, the oxidation stabilities of fish oils and other oils and fats having extremely low oxidative stability cannot be sufficiently enhanced by only such combinations of antioxidants and synergists.

[0008] Dibutylhydroxytoluene (BHT), butylhydroxyanisole (BHA), gallic acid, propyl gallate, tocopherols, and the like are approved as antioxidants for oils and fats and food containing oil or fat, in order to prevent oils and fats from oxidizing. In medical drugs and the like, synthetic antioxidants are used, such as BHT, BHA, TBHQ, and ethoxyquin.

[0009] Sesame oil is relatively stable to oxidation, and it has been known since a long time ago that sesame contains antioxidative components, such as sesamol and other lignans (Japanese Unexamined Patent Application Publication No. 58-132076; Shoku no Kagaku, 225 (11) pp. 40-48 (1996); Shoku no Kagaku, 225 (11) pp. 32-36 (1996)).

[0010] Sesamol is an antioxidant for oils and fats and food containing oil or fat, and is approved as a food additive. It is however reported that sesamol is not effective for oils and fats exhibiting extremely low oxidative stability, such as fish oil (NOF Corporation, from fiscal Heisei 4 (1994) to Heisei 8 (1996), DHA Koudo Seisei Chushutsu Gijutsu Kaihatsu Jigyo, Kekka Gaiyou (DHA Koudo Seisei Chushutsu Gijutsu Kenkyu Kumiai) pp. 74-79 (2002)). Sesamol is not used for enhancing the oxidative stability of fish oil.

[0011] Ascorbic acid and ascorbic acid derivatives are also approved as food additives and used as antioxidants for oils and fats and food containing oil or fat. However, they are not effective for oils and fats exhibiting extremely low oxidative stability, such as fish oil, if they are used alone, and even their combined use with tocopherol does not produce satisfactory effects.

[0012] In order to prevent the oxidation of oils and fats, combined use of various types of antioxidant has been attempted. For example, Japanese Unexamined Patent Application Publication No. 2002-142673 has disclosed a lipophilic antioxidant prepared by emulsifying gallic acid, a water-soluble antioxidant, and an oil-soluble antioxidant into a water-in-oil form with a lipophilic emulsifier. In this application, examples of the water-soluble antioxidant include vitamin C, citric acid, chlorogenic acid, their derivatives, sugar-amino reaction products, proanthocyanidin, flavone derivatives, tea extracts, grape seed extracts, and rutin, and examples of the oil-soluble antioxidant include tocopherol, ascorbyl palmitate, sesamol, and γ -oryzanol.

[0013] Effects of antioxidants have been compared for pyrolysis of tocopherol in vegetable oils in Nippon Eiyo Shokuryo Gakkaishi (Journal of Japanese Society of Nutri-

pp. 291-295 (1992), and 45 (3) pp. 285-290 (1992). Although some of the antioxidants use sesamol and an ascorbic acid ester in combination, they do not produce effects particularly superior to other antioxidants. These literatures discuss effects in oxidation of vegetable oils (having 3 or less unsaturated bonds) at high temperatures, but not in oxidation of polyunsaturated fatty acids (having at least three unsaturated bonds) during storage at room temperature; hence different objects are used under different conditions. This is probably because the combination of sesamol and an ascorbic acid ester does not produce superior effects. In addition, the thermal instability of the antioxidants may affect antioxidant properties.

[0014] Demand for oil or fat containing an unsaturated fatty acid is increasingly growing. Accordingly, it is highly desired to solve the problem of oxidative stability, including how to handle the oil or fat, in a strict sense.

DISCLOSURE OF INVENTION

[0015] The object of the present invention is to provide an organic substance, particularly a polyunsaturated fatty acid or its ester, having a double bond with extremely improved oxidative stability.

[0016] The inventors of the present invention have conducted intensive research in order to enhance the oxidative stability of oils and fats (oils and fats containing a high proportion of polyunsaturated fatty acid, such as oils of fish and aquatic animals). As a result, the inventors found that the oxidative stability of oils and fats can be extremely enhanced by adding an antioxidative component of sesame, such as sesamol, an ascorbic acid or ascorbyl fatty acid ester in combination. In addition, the present inventors found that the antioxidant properties of antioxidative sesame component other than sesamol are also extremely enhanced by combination with ascorbic acid or ascorbyl fatty acid ester, and thus accomplished the present invention.

[0017] The main points of the present invention are the composition described in the following (1) to (13).

(1) A composition having oxidative stability comprising: an organic substance having a double bond which contains an antioxidant comprising an antioxidative sesame component and ascorbic acid or an ascorbyl fatty acid ester.

(2) A composition according to (1), wherein the double bond has active methylene, or located at the end of the organic substance.

(3) A composition according to (1), wherein the organic substance having the double bond is a polyunsaturated fatty acid or its salt or ester.

(4) A composition according to (3), wherein the polyunsaturated fatty acid contains at least one of eicosapentaenoic acid and docosahexaenoic acid.

(5) A composition according to (3) or (4), wherein the ester of the polyunsaturated fatty acid is a triglyceride containing the polyunsaturated fatty acid as a constituent, or a lower alcohol ester of the polyunsaturated fatty acid.

(6) A composition according to (3) or (4), wherein the ester of the polyunsaturated fatty acid is added in a form of refined

[0018] (7) A composition according to any one of (1) to (6), wherein the antioxidative sesame component is at least one of the substances represented by peaks detected by high-performance liquid chromatography using an electrochemical detector at elution times of about 2.66, 3.40, 3.84, 4.57, 4.98, 5.82, 7.00, 8.67, 9.84, 11.24, 12.29, 12.49, 13.36, 14.04, 14.32, 14.74, 15.22, 15.60, 15.82, 16.34, 16.98, 18.10, 18.43, and 34.91 minutes.

(8) A composition according to any one of (1) to (6), wherein the antioxidative sesame component is extracted from sesame, sesame oil, or sesame residue, using a solvent, a lipid, or an emulsifier singly or in combination.

[0019] (9) A composition according to any one of (1) to (6), wherein the antioxidative sesame component is at least one selected from the group consisting of sesamol, sesaminol, episesaminol, pinorelinol, epihinorelinol, syringaresinol, samine, sesamololol, and 2,3-di(4'-hydroxy-3'-methoxybenzyl)-2-buten-4-olide.

(10) A composition according to any one of (1) to (9), wherein the ascorbyl fatty acid ester contains ascorbyl palmitate or ascorbyl stearate.

(11) A composition according to any one of (1) to (10), wherein the ascorbic acid or the ascorbyl fatty acid ester is contained in an excessive amount more than the amount soluble in the polyunsaturated fatty acid or its salt or ester.

(12) A composition according to (11), wherein the excessive amount of the ascorbic acid is in a powder or solid form.

(13) A composition according to any one of (1) to (12), further comprising tocopherol.

(14) A food containing the composition as set forth in any one of (1) to (13).

(15) A powdered oil or fat containing the composition as set forth in any one of (1) to (13).

(16) A powdered baby milk containing the composition as set forth in any one of (1) to (13).

(17) A health food containing the composition as set forth in any one of (1) to (13).

ADVANTAGES

[0020] The present invention can extremely enhance the oxidative stability of a composition containing an organic substance with low oxidative stability which has a double bond having active methylene, or a double bond at its end, particularly containing a polyunsaturated fatty acid. The present invention can make easy the addition of a composition containing a polyunsaturated fatty acid to medical drugs, cosmetic preparations, food, and the like, which has been conventionally limited. Also, the content of such a composition can be increased. Since the antioxidative sesame component and ascorbic acid or an ascorbyl fatty acid ester used in the present invention have been ingested as food for a long time, a safe antioxidant can be provided for food as well.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] FIG. 1 shows amounts of oxygen absorbed by oil

[0022] FIG. 2 shows amounts of oxygen absorbed by oil or fat in Example 2.

[0023] FIG. 3 shows amounts of oxygen absorbed by oil or fat in Example 3.

[0024] FIG. 4 shows amounts of oxygen absorbed by oil or fat in Example 4.

[0025] FIG. 5 shows amounts of oxygen absorbed by oil or fat in Example 5.

[0026] FIG. 6 is a high-performance liquid chromatographic chart of sesame residue extract 1, obtained with an electrochemical detector in Example 6.

[0027] FIG. 7 shows changes with time in the amount of oxygen absorbed by samples of Example 6.

[0028] FIG. 8 shows changes with time in the malondialdehyde content in samples of Example 7.

[0029] FIG. 9 shows changes with time in the alkenal content in samples of Example 7.

[0030] FIG. 10 shows changes with time in the amounts of oxygen absorbed by a sample (sesamol, 0.5%) and the remaining amounts of antioxidants in Example 8.

[0031] FIG. 11 shows changes with time in the amounts of oxygen absorbed by a sample (sesamol, 1.0%) and the remaining amounts of antioxidants in Example 8.

[0032] FIG. 12 shows changes with time in the amounts of oxygen absorbed by samples and the remaining amounts of antioxidants in the case where ascorbyl palmitate was added after 4 days in Example 8.

[0033] FIG. 13 shows changes with time in the PV of samples of Example 9.

[0034] FIG. 14 shows comparison in antioxidant property between BHT and the antioxidant preparation according to the present invention.

BEST MODE FOR CARRYING OUT THE INVENTION

[0035] The organic substance having a double bond, used in the present invention is liable to naturally oxidize even under storage at room temperature. For example, the organic substance has a double bond having active methylene, or a double bond at its end. Examples of such substances include unsaturated fats and polymer materials (monomers). Among the unsaturated fats, polyunsaturated fatty acids having at least four double bonds are particularly easily oxidized, and accordingly conventionally used antioxidants cannot sufficiently prevent the oxidation.

[0036] The polyunsaturated fatty acid or its salt or ester used herein refers to a polyunsaturated fatty acid, a lower alcohol ester of the polyunsaturated fatty acid, and a triglyceride containing the polyunsaturated fatty acid as a constituent. Its examples include oils of fish and aquatic animals containing a high proportion of eicosapentaenoic acid, docosahexaenoic acid, or the like, and their esters, such as eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester. The polyunsaturated fatty acid refers to a fatty acid having 3 or more double bonds. Fatty acids having 4 or more double bonds are particularly effective. Exemplary

include α -linolenic acid, arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid. Also, polyunsaturated fatty acid-based compounds used in the present invention include esters of such fatty acids, such as methyl esters, ethyl esters, triglycerides, ditriglycerides, and monoglycerides.

[0037] Eicosapentaenoic acid is a generic name of fatty acids having a carbon number of 20 and five double bonds, and natural eicosapentaenoic acids are cis-type pentavalent straight-chain unsaturated n-3 fatty acids having double bonds at the 5, 8, 11, 14, and 17 positions. Docosahexaenoic acid is a straight-chain hexenoic acid having a carbon number of 22 and cis-double bonds at the 4, 7, 10, 13, 16, and 19 positions. These EPAs and DHAs derived from nature are contained in natural oils and fats, particularly in oils and fats of marine products, such as tuna, bonito, chub mackerel, sardine, and pacific cod. They may be present in a form of glyceride or other derivatives.

[0038] In the present invention, any material can be used as long as it results in an oil or fat containing a polyunsaturated fatty acid having 3 or more double bonds. Examples of the material for oil or fat containing the polyunsaturated fatty acid include marine fish, such as sardine, chub mackerel, saury, tuna, and bonito; and fats derived from micro-organisms; crustaceans, such as euphausiid and shrimp and lobster; fish oil; animal and vegetable oils; and genetically modified vegetable oils.

[0039] The polyunsaturated fatty acid having 3 or more double bonds can be concentrated by wintering or enzymatically treating oil or fat containing the polyunsaturated fatty acid. Alternatively, the oil or fat containing a polyunsaturated fatty acid having 3 or more double bonds may be esterified with alcohol or hydrotreated to fatty acid, and then subjected to distillation, urea addition, column treatment, enzymatic treatment, or supercritical carbon dioxide treatment. Thus, the polyunsaturated fatty acid can be concentrated.

[0040] The antioxidant used in the present invention does not reduce substances that have been already oxidized. It is therefore necessary that oxides be removed from the organic substance having a double bond before adding the antioxidant. For a polyunsaturated fatty acid or its salt or ester, it is also necessary to remove oxides by degumming, deacidification, decolorization, deodorization, or the like. Preferably, the organic substance is refined to a PV of 3.0 meq/kg or less and an AV of 1.0 or less, and has no odor in terms of sensory testing.

[0041] The antioxidant used in the present invention does not reduce substances that have been already oxidized. It is therefore desired the organic substance to be added has a high refining degree as much as possible by removing oxides. Since odors resulting from oxidation are generated even by slight oxidation, it is necessary to sufficiently refine the organic substance before adding the antioxidant. If refined fish oil is used, it is preferably refined to a PV of 3.0 meq/kg or less and an AV of 1.0 or less so as to be odorless in terms of sensory testing.

[0042] Oil or fat constituted of the unsaturated fatty acid contained in the composition of the present invention may be acidified by hydrolysis or oxidation. The oxidation produces hydroperoxides and decomposition products of the

[0043] For example, soybean oil is oxidized to produce propionaldehyde, 2-pentenal, caproic aldehyde, acetaldehyde, and crotonaldehyde. These oxidation products from the polyunsaturated fatty acid are causes of disagreeable odors of fish oil, and thus a fishy odor peculiar to fish oil is generated. Refined oils containing the unsaturated fatty acid, such as fish oil, soybean oil, linseed oil, and rape-seed oil, may generate disagreeable odor or change in color in the very early stages of their oxidation. This phenomenon is called "Modori" (deterioration). The "Modori" phenomenon in color of decolorized refined vegetable oil is caused by an oxidation product from vitamin E, chromane-5,6-quinone. The present invention is intended to prevent the unsaturated fatty acid from oxidizing, and produces remarkable effects particularly in animal oil having a low oxidative stability.

[0044] The organic substance having a double bond, used in the present invention may be provided in form of tape, poultice, or adhesive tape that contains a medical drug using a polymer having a double bond as the base material. Accordingly, the present invention can be applied to rubber polymers, such as butadiene rubber, styrene butadiene rubber, butyl rubber, chloroprene rubber, acrylic rubber, natural rubber, isoprene rubber, and styrene-isoprene-styrene block copolymer. The composition of the present invention may be used in combination with an antioxidant generally used in these rubber polymers.

[0045] The antioxidative sesame component used in the present invention may be of phenol form. Examples such antioxidative components include sesamol, sesaminol, episesaminol, pilsinol, epihinorelinol, syringaresinol, samine, sesamolinalol, and 2,3-di(4'-hydroxy-3'-methoxybenzyl)-2-buten-4-olide. In FIG. 6, the peaks of the HPLC chart, which were detected by an electrochemical detector, represent their respective antioxidative components. This chart shows that sesame contains many antioxidative components. While these components, including sesamol, can produce a satisfactory effect independently, mixtures of these components exhibit stronger antioxidant properties. The antioxidative sesame components may be used singly or in combination.

[0046] Hence, the antioxidative sesame component used in the present invention may be highly purified antioxidative component from sesame, or a lightly purified antioxidative component including sesamol, which is also containing the other substance derived from sesame, such as sesame lignan, or tocopherol. The antioxidative sesame component may be synthesized. Furthermore, sesame oil may be used as it is, as long as there is no problem with the odor peculiar to sesame oil.

[0047] Specifically, the antioxidative component can be extracted from sesame seeds, sesame oil, or degreased sesame residue after expressing sesame oil. Alternatively, it can be obtained from scum, which is a component prepared by distillation during deodorization of sesame oil. Preferably, roasted sesame is used because the antioxidative component is increased by roasting. Since non-roasted sesame contains a certain proportion of antioxidative component, it can also be used. For extraction from sesame seeds, it is preferable that the principal constituent or neutral lipid be expressed, or removed with a nonpolar solvent, such as

application is limited because the absolute quantity of the neutral lipid is high and, accordingly, the antioxidative component content is low.

[0048] The sesame extract used in the present invention may be prepared by any method, as long as antioxidative components such as represented by HPLS peaks shown in FIG. 6 can be extracted. For example, the antioxidative components can be extracted by use of a solvent, a lipid, or an emulsifier. More specifically, the antioxidative components can be extracted from sesame, sesame oil, or sesame residue by use of organic solvents, such as nitrous oxide, acetone, ethanol, ethyl methyl ketone, glycerol, ethyl acetate, methyl acetate, diethyl ether, cyclohexane, dichloromethane, 1,1,1,2-tetrafluoroethane, 1,1,2-trichloroethane, carbon dioxide, 1-butanol, 2-butanol, butane, 1-propanol, 2-propanol, propane, propylene glycol, hexane, and methanol; lipids, such as triglyceride, diglyceride, and monoglyceride; and emulsifiers, such as propylene glycol fatty acid esters, polyglycerol fatty acid esters, and sorbitan fatty acid esters. In addition, after removal of the solvent by evaporation, the extract is redissolved in an organic solvent. Then, water-soluble constituents are removed by partition with water, or insoluble constituents are removed by filtration. Thus, the antioxidative component can be concentrated.

[0049] In the present invention, the amount of antioxidant used in the external composition can be varied depending on the storage conditions and period or the base material used. If sesamol of sesame is used as the antioxidant, a content of 0.5% or more to the polyunsaturated fatty acid is effective. 1% or more is preferable. Although at most about 0.1% of ascorbyl fatty acid ester can be dissolved in the polyunsaturated fatty acid, it can be appropriately increased according to the application because the duration of antioxidant properties can be enhanced by adding an excessive amount of the antioxidant. For example, a composition prepared by adding 0.1% of sesamol and 0.1% of ascorbyl palmitate to refined fish oil can be preserved for 2 to 3 months at room temperature under open conditions.

[0050] Examples of the ascorbic acid or ascorbyl fatty acid ester used in the present invention include ascorbic acid and ascorbyl fatty acid esters such as ascorbyl palmitate and ascorbyl stearate. As an alternative to these materials, salts of ascorbic acid can also be used. Preferred are materials having a high solubility in lipids.

[0051] In the case of use of the ascorbic acid or ascorbyl fatty acid ester among antioxidants used in the present invention, the antioxidant properties can be further maintained by using an excessive amount of the antioxidant more than its soluble amount. Since it is considered that the antioxidant used for oil or fat is not effective unless it is dissolved, an amount of antioxidant more than saturated concentration is not generally added. However, as shown in Examples 11 and 12, the antioxidant properties can be further maintained by adding an excessive amount of ascorbic acid or an ascorbyl fatty acid ester, rather than by adding a saturated concentration. The presence of an excessive amount of ascorbic acid or ascorbyl fatty acid ester is effective even if the antioxidative sesame component is constant. The excessive amount of ascorbic acid or ascorbyl fatty acid ester is effective irrespective of whether it is in

[0107] sesamol (0.5%)+ascorbyl palmitate (0.1%)

[0108] sesamol (1.0%)+ascorbyl palmitate (0.1%)

[0109] After 4 mL of the samples were placed separately in respective 30 mL brown bottles and hermetically sealed with septums, the samples were stored at 60° C. The concentration of oxygen during storage was measured by gas chromatography, and thus the amount of oxygen reacted with (absorbed by) the oil was calculated. Also, the remaining antioxidant contents were analyzed by HPLC with an electrochemical detector.

[0110] The results are shown in FIGS. 10 and 11. The figures show that, in either case, ascorbyl palmitate was consumed (oxidized) to be lost first, and then the refined fish oil, δ -tocopherol, and sesamol simultaneously started oxidizing. It is therefore assumed that ascorbyl palmitate plays an important role when the antioxidant preparation contains δ -tocopherol, sesamol, and ascorbyl palmitate. In order to confirm this assumption, 0.1% of ascorbyl palmitate was further added to the same system as in FIG. 11 on day four. The results are shown in FIG. 12. FIG. 11 shows that the oil was not oxidized until ascorbyl palmitate was consumed (around day ten); FIG. 12, in which ascorbyl palmitate was added on day four, shows that oxidation of the oil was continuously suppressed even after day ten.

[0111] Thus, it has been shown that it is important that ascorbyl palmitate is present in the antioxidant system of the present invention.

Example 12

<Tests for Effect on Eicosapentaenoic Acid Ethyl Ester of the Present Invention, and for Effect of Excessive Amount of Ascorbyl Palmitate>

[0112] Samples were prepared by adding the following antioxidant preparations separately to eicosapentaenoic acid ethyl ester with a purity of 99% (containing 0.2% of α -tocopherol)

[0113] sesamol (1.0%)+ascorbyl palmitate (0.1%)

[0114] sesamol (1.0%)+ascorbyl palmitate (0.5%)

[0115] Each sample was stored at 60° C., and the peroxide value (PV) was measured.

[0116] The results are shown in FIG. 13. The antioxidant property of the antioxidant preparation containing an excessive amount of ascorbyl palmitate (0.5%) was maintained in comparison with that of the antioxidant preparation containing a soluble amount of ascorbyl palmitate (0.1%).

Example 13

<Comparison with Antioxidant (t-Butylhydroxytoluene (BHT)) Generally Used in External Preparations>

[0117] The antioxidant preparation of the present invention was compared with t-butylhydroxytoluene (BHT), which is an antioxidant generally used. Samples were prepared by adding 0.5%, 1.5%, or 10.0% of BHT, or 1.0% of sesamol and 0.5% of ascorbyl palmitate to refined fish oil (sardine oil) containing 0.5% of δ -tocopherol. To 30 mL brown bottles, 4 mL of the samples were placed separately. The bottles were hermetically sealed with septums and

was measured with time by gas chromatography and thus the amount of oxygen reacted with (absorbed by) the oil was calculated.

Results

[0118] FIG. 14 shows the comparison of the antioxidant properties between BHT and the antioxidant preparation of the present invention. The results show that the antioxidant preparation of the present invention exhibited higher antioxidant property than the same amount (1.5%) of BHT as the total amounts of the antioxidants in the antioxidant preparation of the present invention, and also than a much larger amount (10.0%) of BHT.

INDUSTRIAL APPLICABILITY

[0119] The present invention can provide oils and fats having oxidative stability far superior to known oils and fats containing a polyunsaturated fatty acid. Consequently, when a polyunsaturated fatty acid is added to food, medical drugs, and the like for health promotion, such products can be easily produced and preserved. Also, the types of food to which the composition is added and the polyunsaturated fatty acid content can be easily increased. Specifically, general-purpose refined fish oil containing EPA and DHA can be provided for health food or the like.

1. A composition having oxidative stability comprising: an organic substance having a double bond which contains an antioxidant comprising an antioxidative sesame component which is purified from sesame or synthesized and ascorbic acid or an ascorbyl fatty acid ester.

2. A composition according to claim 1, wherein the double bond has active methylene, or located at the end of the organic substance.

3. A composition according to claim 1, wherein the organic substance having the double bond is a poly unsaturated fatty acid or its salt or ester.

4. A composition according to claim 3, wherein the poly unsaturated fatty acid contains at least one of eicosapentaenoic acid and docosahexaenoic acid.

5. A composition according to claim 3, wherein the ester of the poly unsaturated fatty acid is a triglyceride containing the poly unsaturated fatty acid as a constituent, or a lower alcohol ester of the poly unsaturated fatty acid.

6. A composition according to claim 3, wherein the ester of the poly unsaturated fatty acid is added in a form of refined fish oil.

7. A composition according to claim 1, wherein the antioxidative sesame component is at least one of the substances represented by peaks detected by high-performance liquid chromatography using an electrochemical detector at elution times of about 2.66, 3.40, 3.84, 4.57, 4.98, 5.82, 7.00, 8.67, 9.84, 11.24, 12.29, 12.49, 13.36, 14.04, 14.32, 14.74, 15.22, 15.60, 15.82, 16.34, 16.98, 18.10, 18.43, and 34.91 minutes.

8. A composition according to claim 1, wherein the antioxidative sesame component is extracted from sesame, sesame oil, or sesame residue, using a solvent, a lipid, or an emulsifier singly or in combination.

9. A composition according to claim 1, wherein the antioxidative sesame component is at least one selected from

pinoresinol, epipinoresinol, syringaresinol, samine, sesamol, and 2,3-di(4'-hydroxy-3'-methoxybenzyl)-2-buten-4-olide.

10. A composition according to claim 1, wherein the antioxidative sesame component is sesamol.

11. A composition according to claim 1, wherein the antioxidative sesame component is extracted from sesame residue.

12. A composition according to claim 11, wherein the antioxidative sesame component extracted from sesame residue is extraction using a solvent, a lipid, or an emulsifier singly or in combination.

13. A composition according to claim 1, wherein the ascorbyl fatty acid ester contains ascorbyl palmitate or ascorbyl stearate.

14. A composition according to claim 1, wherein the ascorbic acid or the ascorbyl fatty acid ester is contained in

an excessive amount more than the amount soluble in the poly unsaturated fatty acid or its salt or ester.

15. A composition according to claim 14, wherein the excessive amount of the ascorbic acid is in a powder or solid form.

16. A composition according to claim 1, further comprising tocopherol.

17. A food containing the composition as set forth in claim 1.

18. A powdered oil or fat containing the composition as set forth in claim 1.

19. A powdered baby milk containing the composition as set forth in claim 1.

20. A health food containing the composition as set forth in claim 1.

* * * * *

ANEXO 2



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(54) **PHARMACEUTICAL DOSAGE FORMS FOR HIGHLY HYDROPHILIC MATERIALS**

Jun. 8, 2001, which is a continuation-in-part of application No. 09/345,615, filed on Jun. 30, 1999, now Pat. No. 6,267,985.

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(57) **ABSTRACT**

Pharmaceutical dosage forms having a highly hydrophilic fill material and a shell encapsulating the fill material are disclosed and described. Generally, the shell has at least one plasticizing agent therein in order to provide the shell with an effective plasticity. In one aspect, the shell may have included therein an amount of plasticizing agent that is sufficient to provide the shell with an effective plasticity upon migration of a portion of the plasticizing agent into the fill material. In another aspect, the plasticizing agent may have a solubility in the fill material of less than about 10% w/w. In yet another aspect, a combination of a plasticizing agent, and a plasticizing agent having a solubility in the fill material of less than about 10% w/w, may be presented in a total amount sufficient to provide the shell with an effective plasticity upon migration of plasticizing agent into the fill material.

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Related U.S. Application Data

(63) Continuation-in-part of application No. 09/898,553, filed on Jul. 2, 2001, now Pat. No. 6,451,339, which is a continuation of application No. 09/258,654, filed on Feb. 26, 1999, now Pat. No. 6,294,192. Continuation-in-part of application No. 09/877,541, filed on

PHARMACEUTICAL DOSAGE FORMS FOR HIGHLY HYDROPHILIC MATERIALS

PRIORITY DATA

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/898,553, filed on Jul. 2, 2001, which is a continuation of U.S. patent application Ser. No. 09/258,654, filed Feb. 26, 1999, now issued as U.S. Pat. No. 6,294,192. This application is also a continuation-in-part of U.S. patent application Ser. No. 09/877,541, filed on Jun. 8, 2001, which is a continuation of U.S. patent application Ser. No. 09/345,615, filed on Jun. 30, 1999, now issued as U.S. Pat. No. 6,267,985. Each of the above-recited patents and patent applications, as well as each of the additional references set forth in this patent application are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to pharmaceutical dosage forms that include a highly hydrophilic fill material and shell that encapsulates the fill material. Accordingly, the present invention involves the fields of chemistry, pharmaceutical sciences, and medicine.

BACKGROUND

[0003] Oral capsules are a well-known dosage form for administering various agents into the body through the gastrointestinal tract. Generally speaking, such capsules have two basic components, namely, a fill material that includes a pharmaceutically active agent, and a shell that encapsulates the fill material. Upon administration, the fill material is released and absorbed by the body as the shell degrades under various digestive forces.

[0004] Many specific constituents have been used to form the shell of various capsule formulations. One basic component is a matrix, or film forming material, such as gelatin, hydroxypropyl methyl cellulose (HPMC), gums, or other polymeric materials. Other, additives are often included in the shell to control the physical characteristics thereof. One such additive is a plasticizing agent that is used to control the softness or pliability of the shell. Regardless of whether the shell is prepared to be a hard or soft shell, certain amounts of plasticizing agents are important in order to keep the shell from becoming overly brittle.

[0005] Since its first inception, the concept of a capsule dosage form has evolved to include a variety of specific formulations which attain certain desired physical and performance properties. For example, in addition to a solid fill material, liquid or semi-solid fills have been employed in order to enable a more rapid release and an increased absorption of the pharmaceutically active agent. Further, both hard and soft shells have been used in order to vary the release timing of the pharmaceutically active agent. In short, by the variation of the shell and fill material constituents, improved capsule dosage forms have been produced.

[0006] One common constituent of the fill material is a carrier, or vehicle in which the pharmaceutically active agent to be delivered is dissolved or dispersed. Traditionally, fat soluble vitamins, such as vitamin E and digestible oils, such as triglycerides and fatty acids have been employed as the major constituent either as the active ingredient itself or

as the carrier or vehicle for dissolving or dispersing the active ingredient. In general, these non-hygroscopic and non-glycerol solubilizing materials enjoy good compatibility with traditional gelatin capsule shells that utilize glycerol as the plasticizer. However, the performance of these dosage forms frequently suffer from inconsistent and poor absorption of the active ingredients due to the lack of water dispersibility of such fill materials in vivo.

[0007] As a result, many types of carriers with improved water dispersibility have been sought and used. One class of vehicle that has been used in the fill is liquid polyethylene glycols (PEG) with a molecular weight of 100-600. However, since PEG is not a surfactant, it provides insufficient solubilization for a wide range of active ingredients once administered to the GI tract. Further, these materials suffer from the disadvantage of making the capsules brittle upon storage because their hygroscopic nature tend to draw water and other constituents, such as plasticizers out of the shell over time, as reported in U.S. Pat. Nos. 4,744,988 and 4,780,316.

[0008] Excessive brittleness interferes with the functionality of capsule dosage forms in a number of ways. First, an excessively brittle capsule may actually crack or burst prior to administration, thus allowing the fill material to leak therefrom. Further, a capsule that is too brittle may take too long to dissolve in gastric juices, and therefore the encapsulated active ingredient may not be released and absorbed as it intended to be. These and other issues caused by capsule embrittlement most often render the dosage form useless and a embrittlement inhibiting composition is required to impart physical stability and durability to the capsule.

[0009] Another problem that has been recognized with many fill materials, such as 1,2-propylene glycols, is their propensity to migrate into the shell, and thus overly soften it. One example of this phenomenon is contained in U.S. Pat. No. 5,985,321. Overly softened shells experience a several performance disadvantages, and further, the loss of propylene glycol from the fill material may upset an established balance of constituents that is required for sufficient drug loading capacity of the formulation and proper delivery and absorption of the active ingredient in the gastrointestinal tract. Therefore, propylene glycol was added to the shell as well to counteract the migration of it from the fill.

[0010] As a result, capsule dosage forms that include a fill material containing constituents capable of holding and delivering a wide variety of drugs, such as hygroscopic and hydrophilic carriers, that limit the movement of constituents from the shell into the fill material, and from the fill material into the shell, thus maintaining desired shell integrity and performance, continue to be sought through ongoing research and development efforts.

SUMMARY OF THE INVENTION

[0011] Accordingly, the present invention encompasses pharmaceutical dosage forms having a highly hydrophilic fill material that is encapsulated by a shell which maintains an effective plasticity despite the hydrophilicity of the fill material.

[0012] In one aspect, the dosage form may include a fill material may having a carrier of at least about 40% w/w of a hydrophilic surfactant, and at least one pharmaceutically

active agent, and a shell encapsulating the fill material which contains at least one plasticizing agent in an amount sufficient to maintain an effective shell plasticity upon migration of a portion of the plasticizing agent into the fill material.

[0013] In another aspect, the dosage form may include a fill material having a carrier of at least about 40% w/w of a hydrophilic surfactant, and at least one pharmaceutically active agent, and a shell encapsulating the fill material which contains an effective amount of a plasticizing agent having a solubility of less than 10% w/w in the fill material.

[0014] In yet another aspect of the invention, the dosage form may include a fill material having a carrier of at least about 40% w/w of a hydrophilic surfactant, and at least one pharmaceutically active agent, and a shell encapsulating the fill material, said shell containing a first plasticizing and a second plasticizing agent, said second plasticizing agent having a solubility in the fill material of less than about 10% w/w agent, wherein the first and second plasticizing agents are present in amounts sufficient to maintain an effective shell plasticity upon migration of a portion of either plasticizing agent into the fill material.

[0015] It is also an aspect of the present invention that the plasticizing agent(s) is present in an amount that the disintegration of the dosage form and/or the release of the fill material is not significantly altered (becomes slower or incomplete) after storage.

[0016] It is another aspect of the present invention that the plasticizing agent(s) is present in an amount that the disintegration of the dosage form and/or the release of the fill material is not significantly altered (becomes slower or incomplete) after storage, even if there is any chemical degradation or denaturation occurring in the shell, such as crosslinking of gelatin capsules by aldehyde substances.

[0017] There has thus been outlined, rather broadly, various features of the present invention so that the detailed description thereof that follows may be better understood, and so that the present contribution to the art may be better appreciated. Other features of the present invention will become clearer from the following detailed description of the invention, taken with the accompanying claims, or may be learned by the practice of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] FIG. 1 is a graphical representation of release rate testing results achieved by oral dosage forms containing a highly hydrophilic fill material as used in the present invention, and traditional shell compositions used for moderately to low hydrophilic materials, such as PEG, following storage under varying conditions for a period of 4 weeks, as compared to freshly made conventional oral dosage forms.

DETAILED DESCRIPTION OF THE INVENTION

[0019] Before the present pharmaceutical dosage forms are disclosed and described, it is to be understood that the present invention is not limited to the particular process steps and materials disclosed herein, but is extended to equivalents thereof as would be recognized by those ordinarily skilled in the relevant arts. It should also be understood that terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting.

[0020] Definitions

[0021] In describing and claiming the present invention, the following terminology will be used.

[0022] The singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to a fill material containing "a hydrophilic carrier" includes one or more hydrophilic carriers, reference to "an additive" includes reference to one or more of such additives, and reference to "the plasticizing agent" includes reference to one or more of such agents.

[0023] The terms "composition" and "formulation" may be used interchangeably herein.

[0024] As used herein, "matrix forming material" and "film forming material" may be used interchangeably, and refer to materials that are known to those of ordinary skill in the art as suitable for use in forming a shell of a typical capsule dosage form. Examples of such materials include without limitation, various gelatins, hydroxypropyl methyl cellulose (HPMC), starches, polymers, and gum acacia.

[0025] As used herein "shell" refers to a barrier that encapsulates, surrounds, or encompasses at least a portion of a material or an object. In the pharmaceutical arts, capsule dosage forms are well known to include a shell as an essential component that surrounds a fill material. A variety of specific materials and methods for the formation of such shells, are well known to those of ordinary skill in the art.

[0026] As used herein, an "effective amount," and "sufficient amount" may be used interchangeably, and refer to an amount of a substance that is sufficient to achieve an intended purpose or objective. For example, a sufficient, or effective amount of a suspending agent would be the minimum amount of agent required to effectively suspend one substance, such as a pharmaceutically active agent, in a carrier. The determination of an effective amount is well within the ordinary skill in the art of pharmaceutical, neurochemical, herbaceutical, cosmetic, and medical sciences. See, for example, Meiner and Tonascia, "Clinical Trials: Design, Conduct, and Analysis," *Monographs in Epidemiology and Biostatistics*, Vol. 8 (1986).

[0027] As used herein, "pharmaceutically active agent," "bioactive agent," "therapeutic agent," "active agent," and "drug" may be used interchangeably herein, and refer to a substance, such as a chemical compound or complex, that has a measurable beneficial physiological effect on the body, such as a therapeutic effect in treatment of a disease or disorder, when administered in an effective amount. Further, when these terms are used, or when a particular active agent is specifically identified by name or category, it is to be understood that such recitation is intended to include the active agent per se, as well as pharmaceutically acceptable, pharmacologically active derivatives thereof, or compounds significantly related thereto, including without limitation, salts, esters, amides, prodrugs, active metabolites, isomers, fragments, analogs, etc.

[0028] Concentrations, amounts, solubilities, particle size, wavelength, and other numerical data may be expressed or presented herein in a range format. It is to be understood that such a range format is used merely for convenience and brevity and thus should be interpreted flexibly to include not only the numerical values explicitly recited as the limits of

the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly recited.

[0029] As an illustration, a concentration range of "about 4% w/w to about 60% w/w" should be interpreted to include not only the explicitly recited concentration of about 4% w/w to about 60% w/w, but also include individual concentrations and the sub-ranges within the indicated range. Thus, included in this numerical range are individual concentrations such as 4% w/w, 10% w/w, 23% w/w, and 46% w/w, and sub-ranges such as from 10% w/w to 50% w/w, from 20% w/w to 40% w/w, from 25% w/w to 35% w/w, from 15% w/w to 20% w/w, etc.

[0030] This same principle applies to ranges reciting only one numerical value. Furthermore, such an interpretation should apply regardless of the breadth of the range or the characteristics being described.

[0031] Invention

[0032] Applicants have discovered pharmaceutical dosage forms having a shell that retains an effective plasticity while encapsulating a highly hydrophilic fill material. Such dosage forms present a number of advantages including increased freedom in formulating, processing and manufacturing specific dosage forms, increased absorption and/or efficacy of the active ingredient, more consistent performance of the dosage form with respect to disintegration of the dosage and dissolution/ solubilization of the active ingredient and improved storage stability.

A. Shell Formulations

[0033] The shell of the present invention may be either a hard or soft capsule shell, and includes a number of fundamental constituents as will be recognized by those of ordinary skill in the art, namely a matrix forming material, and at least one plasticizing agent. A wide variety of matrix forming materials are suitable for use in the dosage forms of the present invention, and the selection of specific materials may be based, at least in part, on factors such as the specific results to be achieved. Examples of specific materials include without limitation, gelatins, including type A gelatins, such as the gelatin derived from acid-treated pigskins, and type B gelatins, such as those derived from alkali-treated bovine bones and hides, hydroxypropyl methylcellulose (HPMC), starches, and gum acacia. Other specific matrix forming materials that may be particularly desired in view of a given overall dosage form can be determined by those of ordinary skill in the art.

[0034] The specific amount of matrix forming material used in the shell formulation may be determined in part by a variety of factors, including the type of shell to be formed (i.e. hard or soft), and by the amount and type of other constituents or additives that are to be included in the shell. However, in one aspect, the amount of matrix forming material may be from about 20% w/w to about 70% w/w of the shell. In another aspect, the amount may be from about 30% w/w to about 50% w/w of the shell.

[0035] Many plasticizing agents are known, and may also be used in the shell of the present dosage form. One basis for selecting a particular plasticizing agent may be the solubility of that agent in a specific hydrophilic fill material to be used. In one aspect, the plasticizing agent may have a solubility of

less than about 10% w/w in the fill material. In another aspect, the solubility of the plasticizing agent in the fill material may be less than about 5% w/w. In yet another aspect, the solubility may be less than about 1% w/w. In a further aspect, the solubility of the plasticizing agent may be less than about 0.5% w/w. Lowered solubility in the specific hydrophilic fill material substantially impedes the migration of the plasticizing agent out of the shell and into the fill material. Examples of specific plasticizing agents displaying such limited solubilities in many hydrophilic surfactant materials include without limitation: sorbitol, sorbitanes, xylitol, maltitol, maltitol syrup, partially dehydrated hydrogenated glucose syrups, hydrogenated starch hydrolysate, polyhydric alcohols having an equilibrium relative humidity of greater than or equal to 80%, carrageenan, polyglycerol, non-crystallizing solutions of sorbitol, glucose, fructose, glucose syrups, and mixtures and equivalents thereof.

[0036] Whether the plasticizing agent selected and used is one that has a low solubility in the fill material or not, in accordance with one aspect of the invention, the plasticizing agent may be presented in an amount that is sufficient to maintain an effective shell plasticity upon migration of a portion of the plasticizing agent from the shell and into the fill and/or may be present in a sufficient amount to maintain a desirable dissolution/disintegration profile with respect to the rate and the extent release and/or dispersing of the encapsulated active agent in a specific dissolution medium or upon administration inside the GI tract. The exact amount of plasticizing agent required to compensate for the plasticizing agent anticipated to be lost may depend on a variety of factors, such as the specific fill material and solubility of the plasticizing agent therein. However, those of ordinary skill in the art will be able to readily determine approximate amounts required to maintain effective shell plasticity based on the known characteristics presented by a given dosage form, and will further be able to identify specific amounts through routine experimentation with the dosage form. In one aspect of the invention, such an amount of plasticizing agent may be from about 4% w/w to about 60% w/w of the shell. In another aspect, the amount may be from about 10% w/w to about 35% w/w.

[0037] An additional option for maintaining effective shell plasticity and/or a desirable dissolution/disintegration profile of the encapsulated active agent in view of the highly hydrophilic fill material is to include a combination of plasticizing agents in the shell in a total amount sufficient to maintain effective shell plasticity upon migration of a portion of either or both agents into the fill material. In one aspect of the invention, such a combination may include a first plasticizing agent, and a second plasticizing agent having a limited solubility in the fill material as recited above. The total amounts and ratios of each ingredient required to maintain an effective plasticity may be determined by one of ordinary skill in the art in the manners already indicated. While a variety of ratios and amounts are contemplated, in one aspect, the total amount of combined plasticizing agent may be within the ranges already established for plasticizing agents herein.

[0038] In addition to the components of a matrix forming material and the at least one plasticizing agent, the shells used in the dosage forms of the present invention may include additional additives as required, in order to achieve a specifically desired formulation or result. Examples of

Example 8

[0235]

a) Fill composition	(% by weight)
Progesterone	12 (8 parts suspended)
Estradiol	0.1
TPGS	21
Cremophor EL	24
Labrafil M2125CS	20
α -tocopherol	11
Propylene Glycol	8
Water	4
b) Shell (dry) composition	(% by weight)
Gelatin	50
Starch	15
Maltitol Syrup	25
Water	10

Example 9

[0236]

a) Fill composition	(% by weight)
Ondansetron	2
Cremophor RH40	40
Capmul MCM	20
PEG 400	20
Propylene Glycol	8
Ethanol	10
b) Shell composition for encapsulation (Wet)	(% by weight)
Gelatin	35
Gum Acacia	9
Glycerin	7
Sorbitol solution	18
Maltitol solution	6
Water	25

Example 10

[0237]

a) Fill composition	(% by weight)
Sumatriptan	10 (9 parts suspended)
Cremophor RH40	40
Capmul MCM	28
PEG 400	28
b) Shell composition for encapsulation (Wet)	(% by weight)
Gelatin	42
Sorbitol solution	30
Water	28

Example 11

[0238]

a) Fill composition	(% by weight)
Zolpidem	2 (1.5 parts suspended)
Cremophor RH40	65
PVP K-12	30
Water	3
b) Shell composition for encapsulation (Wet)	(% by weight)
Gelatin	47
Sorbitol solution	6
PEG 200	15
Water	32

Example 12

[0239]

a) Fill composition	(% by weight)
Zaleplon	2 (1.5 parts suspended)
TPGS	70
Propylene Glycol	8
Ethanol	15
Water	5
b) Shell composition for encapsulation (Wet)	(% by weight)
Gelatin	47
Glycerin	10
Sorbitol solution	6
Acetylated monoglyceride	5
Water	32

[0240] It is to be understood that the above-described arrangements are only illustrative of the application of the principles of the present invention. Numerous modifications and alternative arrangements may be devised by those skilled in the art without departing from the spirit and scope of the present invention and the appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been described above with particularity and detail in connection with what is presently deemed to be the most practical and preferred embodiments of the invention, it will be apparent to those of ordinary skill in the art that numerous modifications, including, but not limited to, variations in size, materials, shape, form, function and manner of operation, assembly and use may be made without departing from the principles and concepts set forth herein.

What is claimed is:

1. A pharmaceutical dosage form comprising:

a fill material including a carrier of at least about 40% w/w of a hydrophilic surfactant, and at least one pharmaceutically active agent; and

a shell encapsulating the fill material, said shell containing at least one plasticizing agent in an amount sufficient to maintain an effective shell plasticity upon migration of a portion of the plasticizing agent into the fill material.

2. A pharmaceutical dosage form comprising:
- a fill material including a carrier of at least about 40% w/w of a hydrophilic surfactant, and at least one pharmaceutically active agent; and
 - a shell encapsulating the fill material, said shell containing an effective amount of a plasticizing agent having a solubility of less than 10% w/w in the fill material.
3. The pharmaceutical dosage form of either claim 1 or 2, further comprising a lipophilic coating on an outer surface of the shell.
4. The pharmaceutical dosage form of either claim 1 or 2, wherein the hydrophilic surfactant is a member selected from the group consisting essentially of: non-ionic surfactants having an HLB value of equal to or greater than 10, ionic surfactants, and mixtures thereof.
5. The pharmaceutical dosage form of claim 4, wherein the hydrophilic surfactant is a non-ionic surfactant having an HLB value of equal to or greater than 10.
6. The pharmaceutical dosage form of either claim 1 or 2, wherein the carrier further comprises a lipophilic additive selected from the group consisting essentially of: lipophilic surfactants, triglycerides, and mixtures thereof.
7. The pharmaceutical dosage form of claim 6, wherein the lipophilic additive is a lipophilic surfactant.
8. The pharmaceutical dosage form of claim 7, wherein the lipophilic surfactant is a member selected from the group consisting essentially of: non-ionic surfactants having an HLB value of equal to or less than 10, unionized ionizable surfactants, and mixtures thereof.
9. The pharmaceutical dosage form of claim 8, wherein the lipophilic surfactant is a non-ionic surfactant having an HLB value of equal to or less than 10.
10. The pharmaceutical dosage form of claim 7, wherein the hydrophilic surfactant and the lipophilic surfactant are presented in the carrier at respective amounts such that upon diluting with an aqueous solution, the carrier forms a clear aqueous dispersion.
11. The pharmaceutical dosage form of claim 10, wherein the surfactants are diluted with an aqueous solution at an aqueous solution to carrier ratio of about 100:1 by weight, and the clear aqueous dispersion has an absorbance of less than about 0.3 at 400 nm.
12. The pharmaceutical dosage form of either claim 1 or 2, wherein the at least one pharmaceutically active agent is a lipophilic drug.
13. The pharmaceutical dosage form of either claim 1 or 2, wherein the at least one pharmaceutically active agent is a hydrophilic drug.
14. The pharmaceutical dosage form of either claim 1 or 2, wherein the carrier further comprises at least one additive selected from the group consisting of: antioxidants, buffers, antifoaming agents, detackifiers, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, stabilizing agents, solubilizers, binders, fillers, plasticizing agents, lubricants, and mixtures thereof.
15. The pharmaceutical dosage form of claim 14, wherein the at least one additive is a solubilizer.
16. The pharmaceutical dosage form of claim 15, wherein the solubilizer is a member selected from the group consisting of alcohols, polyols, amides, esters, propylene glycol ethers, and mixtures thereof.
17. The pharmaceutical dosage form of either claim 1 or 2, wherein the pharmaceutically active agent is at least partially suspended in the carrier.
18. The pharmaceutical dosage form of claim 17, wherein the carrier further includes a stabilizing agent.
19. The pharmaceutical dosage form of claim 18, wherein the stabilizing agent imparts increased viscosity to the fill material and retards sedimentation.
20. The pharmaceutical dosage form of claim 19, wherein the stabilizing agent is a member selected from the group consisting essentially of: suspending agents, flocculating agents, thickening agents, gelling agents, buffering agents, antioxidants, preservatives, antimicrobial agents, and mixtures thereof.
21. The pharmaceutical dosage form of claim 19, wherein the stabilizing agent is a suspending agent.
22. The pharmaceutical dosage form of claim 20, wherein the suspending agent is a member selected from the group consisting essentially of: microcrystalline cellulose, sodium carboxymethylcellulose, powdered cellulose, ethymethylcellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, ethylhydroxy ethylcellulose, hydroxypropyl cellulose, attapulgit, bentonite, hectorite, montmorillonite, silica gel, fumed silicon dioxide, colloidal silicon dioxide, acacia, agar, carrageenan, guar gum, locust bean gum, pectin, sodium alginate, propylene glycol alginate, tamarind gum, xanthan gum, carbomer, povidone, sodium starch glycolate, starches, tragacanth, magnesium aluminum silicate, aluminum silicate, magnesium silicate, gelatin, and glycyrrhizin, and mixtures thereof.
23. The pharmaceutical dosage form of either claim 1 or 2, wherein the shell further comprises at least one matrix forming material selected from the group consisting of: gelatin, starch, gum acacia, hydroxypropyl methyl cellulose, and mixtures thereof.
24. The pharmaceutical dosage form of claim 23, wherein the at least one matrix forming material is gelatin.
25. The pharmaceutical dosage form of claim 1, wherein the solubility of the plasticizing agent in the fill material is less than about 10% w/w.
26. The pharmaceutical dosage form of either claim 1 or 25, wherein the solubility of the plasticizing agent in the fill material is less than about 5% w/w.
27. The pharmaceutical dosage form of either claim 1 or 25, wherein the solubility of the plasticizing agent in the fill material is less than about 1% w/w.
28. The pharmaceutical dosage form of either claim 1 or 25, wherein the solubility of the plasticizing agent in the fill material is less than about 0.5% w/w.
29. The pharmaceutical dosage form of either claim 1 or 2, wherein the amount of plasticizing agent in the shell is from about 4% w/w to about 60% w/w of the shell.
30. The pharmaceutical dosage form of either claim 2 or 25, wherein the plasticizing agent is a member selected from the group consisting essentially of: sorbitol, sorbitanes, xylitol, maltitol, maltitol syrup, partially dehydrated hydrogenated glucose syrups, hydrogenated starch hydrolysate, polyhydric alcohols having an equilibrium relative humidity of greater than or equal to 80%, carrageenan, polyglycerol, non-crystallizing solutions of sorbitol, glucose, fructose, glucose syrups, and mixtures and equivalents thereof.

31. The pharmaceutical dosage form of claim 30, wherein the plasticizing agent is a member selected from the group consisting of sorbitol, sorbitanes, maltitol, mannitol, and mixtures thereof.

32. The pharmaceutical dosage form of either claim 1 or 2, wherein the shell further comprises an additive selected from the group consisting of: coloring agents, antioxidant, preservatives, surfactants, and mixtures thereof.

33. The pharmaceutical dosage form of claim 32, wherein the shell additive is a surfactant.

34. The pharmaceutical dosage form of either claim 1 or 2, wherein the dosage form is a capsule.

35. The pharmaceutical dosage form of claim 34, wherein the capsule is a hard capsule.

36. The pharmaceutical dosage form of claim 34, wherein the capsule is a soft capsule.

37. A pharmaceutical dosage form comprising:

a fill material including a carrier of at least about 40% w/w of a hydrophilic surfactant, and at least one pharmaceutically active agent; and

a shell encapsulating the fill material, said shell containing a first plasticizing agent and a second plasticizing agent, said second plasticizing agent having a solubility in the fill material of less than about 10% w/w agent, wherein the first and second plasticizing agents are present in amounts sufficient to maintain an effective shell plasticity upon migration of a portion of either plasticizing agent into the fill material.

* * * * *

PODER ESPECIAL

Yo, **ORLANDO MUÑOZ MARTINEZ**, mayor de edad y vecino de la ciudad de Bogotá (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **LABORATORIOS SYNTHESIS S.A.S.** sociedad legalmente constituida y domiciliada en la ciudad de Bogotá (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, 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. **11 163.902**, titulada "**COMPOSICIÓN FARMACÉUTICA ESTABLE Y MÉTODOS PARA UTILIZAR LA MISMA**", cuyo titular **AMARIN PHARMA, INC.** 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 administrativa 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.

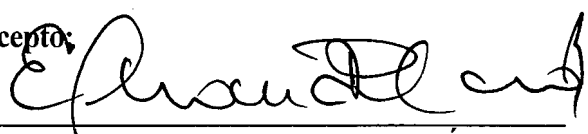
De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

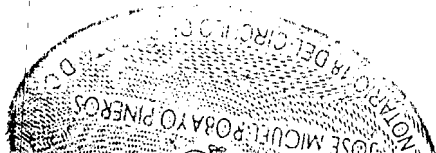
Dado y Firmado en Bogotá (Colombia) a los 04 días del mes de septiembre de 2012.

LABORATORIOS SYNTHESIS S.A.S.


Cédula de ciudadanía No. 8.317.044 de Medellín.
NIT: 860.000.760-1
Representante Legal

Acepto:


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



DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Circuito de Bogotá

quien exhibió C.C.

Expedida en _____ y declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto

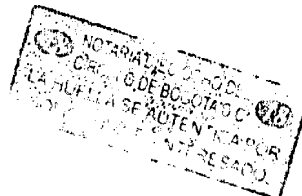
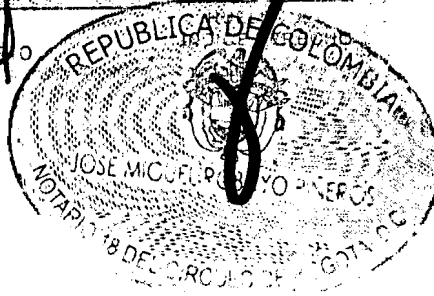
06 SEP 2012

BOGOTÁ D.C.

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CAMARA DE COMERCIO DE BOGOTA

SEDE CENTRO

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PAGINA: 1 de 5

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CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL

CERTIFICA:

NOMBRE : LABORATORIOS SYNTHESIS S A S

N.I.T. : 860000760-1

DOMICILIO : BOGOTA D.C.

CERTIFICA:

MATRICULA NO: 00008059 DEL 23 DE MARZO DE 1972

CERTIFICA:

RENOVACION DE LA MATRICULA :29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO: 2012

ACTIVO TOTAL REPORTADO:\$78,678,599,000

CERTIFICA:

DIRECCION DE NOTIFICACION JUDICIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL DE NOTIFICACION JUDICIAL : lmbautista@synthesis.com.co

DIRECCION COMERCIAL : CRA 44 NO 20C 73

MUNICIPIO : BOGOTA D.C.

EMAIL COMERCIAL : lmbautista@synthesis.com.co

CERTIFICA:

CONSTITUCION: ESCRITURA PUBLICA NO.2078, NOTARIA 8 BOGOTA, DEL 27 DE JULIO DE 1.950, INSCRITA EL 10 DE AGOSTO DE 1.950, BAJO EL NO. 21.766 DEL LIBRO RESPECTIVO ACLARADA POR ESCRITURA NO. 3608 DEL 8 DE OCTUBRE DE 1.956 NOTARIA 8 DE BOGOTA INSCRITA EN ESTA - CAMARA DE COMERCIO EL 19 DE OCTUBRE DE 1.956 BAJO EL NO. 35.547 DEL LIBRO RESPECTIVO, SE CONSTITUYO LA SOCIEDAD DENOMINADA: "LABORATORIOS BALBAG".

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 3997 OTORGADA EN LA NOTARIA 8 DE BOGOTA EL 24 DE NOVIEMBRE DE 1.952, INSCRITA EN ESTA CAMARA DE COMERCIO EL 1 DE DICIEMBRE DE 1.952, BAJO EL NUMERO 26.158 DEL LIBRO RESPECTIVO, LA SOCIEDAD CAMBIO SU NOMBRE DE:"LABORATORIOS BALBAG" POR EL DE "LABORATORIO SYNTHESIS" E INTRODUJO OTRAS REFORMAS.

CERTIFICA :

QUE POR ESCRITURA PUBLICA NUMERO 6491 OTORGADA EN LA NOTARIA 1. - DE BOGOTA EL 24 DE DICIEMBRE DE 1.981, INSCRITA EN ESTA CAMARA DE COMERCIO EL 12 DE MARZO DE 1.982, BAJO EL NUMERO 113.297 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE "LABORATORIOS SYNTHESIS - BALAVOINE Y CIA. S.C.A" POR EL DE "LABORATORIOS SYNTHESIS LTDA. Y CIA. S.C.A" E INTRODUJO OTRAS REFORMAS.

CERTIFICA:

QUE POR ESCRITURA PUBLICA NUMERO 8580 OTORGADA EN LA NOTARIA 3 DE

BOGOTA EL 4 DE DICIEMBRE DE 1.973, INSCRITA EN ESTA CAMARA DE COMERCIO EL 7 DE ENERO DE 1.974, BAJO EL NUMERO 14.478 DEL LIBRO IX, LA SOCIEDAD SE TRASFORMO DE LIMITADA EN COMANDITA POR ACCIONES BAJO EL NOMBRE DE LABORATORIOS SYNTHESIS BALAVOINE Y CIA. S.C.A.

CERTIFICA:

QUE POR ACTA NO. 117 DE LA ASAMBLEA DE ACCIONISTAS, DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NÚMERO 1390261 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA SE TRANSFORMO DE SOCIEDAD EN COMANDITA POR ACCIONES A SOCIEDAD POR ACCIONES SIMPLIFICADA BAJO EL NOMBRE DE: LABORATORIOS SYNTHESIS S.A.S.

CERTIFICA:

QUE POR E.P. NO.5.435 DEL 17 DE SEPTIEMBRE DE 1.996, NOTARIA PRIMERA DE SANTAFE DE BOGOTA, INSCRITA EL 30 DE SEPTIEMBRE DE 1.996, BAJO EL NO.556.909 DEL LIBRO IX, ADICIONADA POR LOS REGISTROS 557 146 DEL 1 DE OCTUBRE DE 1.996, Y 557.301 DEL 2 DE OCTUBRE DE 1996 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA COMUNICO QUE SE FUSIONO, ABSORBIENDO A LA SOCIEDAD "SYNTHESIS VETERINARIA LTDA Y CIA S C A"

CERTIFICA:

QUE POR E.P. NO.1024 DEL 28 DE FEBRERO DE 1997, DE LA NOTARIA 1. DE SANTAFE DE BOGOTA, INSCRITA EL 31 DE MARZO DE 1997, BAJO EL NUMERO 579245 DEL LIBRO IX, CELEBRO ACUERDO DE FUSIÓN CON LA SOCIEDAD PRODUCTOS DIETÉTICAS DIETESYN S.A, DONDE LA SOCIEDAD DE LA REFERENCIA FUE LA ABSORBENTE.

CERTIFICA:

QUE POR ACTA NO. 120 DE LA ASAMBLEA DE ACCIONISTAS DEL 29 DE JULIO DE 2010, INSCRITA EL 19 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01429837 DEL LIBRO IX, LA SOCIEDAD DE LA REFERENCIA (ABSORBENTE) ABSORBE MEDIANTE FUSIÓN A LAS SOCIEDADES INMUNOSYN SAS Y GYNOPHARM SAS LAS CUALES SE DISUELVEN SIN LIQUIDARSE.

CERTIFICA:

REFORMAS:

ESCRITURAS NO.	FECHA	NOTARIA	INSCRIPCION
4471	18-XII-1.956	8 BTA.	22-XII-1.956 NO. 36.077
3322	31-XII-1.958	8 BTA.	12-I-1.959 NO. 42.034
2322	22-IX-1.961	8 BTA.	29-IX-1.961 NO. 51.161
290	2-II-1.967	6 BTA.	24-II-1.967 NO. 71.304
8545	16-XII-1.967	6 BTA.	26-I-1.968 NO. 75.041
4679	20-XII-1.967	8 BTA.	26-I-1.968 NO. 75.042
3010	14-V-1.968	6 BTA.	30-V-1.968 NO. 76.244
2931	4-V-1.970	6 BTA.	18-V-1.970 NO. 84.983
5656	13-VII-1.970	6 BTA.	13-VIII-1.970 NO. 86.126
3487	15-VII-1.971	3 BTA.	29-VII-1.971 NO. 90.980
4638	10-VII-1.984	11 BTA.	27-VIII-1.984 NO.157.001
1443	14-III-1.985	11 BTA.	26- III-1.985 NO.167.627
724	11- II-1.985	1 BTA.	21- II-1.985 NO.165.940
4836	11-VIII-1986	1 BTA.	23- IX -1.986 NO.197.784
5659	15- IX -1986	1 BTA.	23- IX -1.986 NO.197.784
6326	16- X -1987	1 BTA.	23- X -1.987 NO.221.604
5164	21-VIII-1990	1 BTA.	3- IX -1.990 NO.303.579
9244	23-XII- 1991	1 STAFE.BTA.	8-I -1.992 NO.351.255
8145	15- X - 1992	1 STAFE.BTA.	16- X-1.992 NO.382.488
1374	26- III-1993	1 STAFE.BTA.	19- III-1993 NO.399972
3120	01-VI-1.995	1A.STAFE BTA	23-VI- 1.995 NO.498.060
5435	17-IX-1.996	1A.STAFE BTA	30-IX- 1.996 NO.556.909
5435	17-IX-1.996	1A.STAFE BTA	01- X- 1.996 NO.557.146
5435	17-IX-1.996	1A.STAFE BTA	02- X- 1.996 NO.557.301



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5942	7-X -1.996	1A.STAFE BTA 11- X- 1.996	NO.558.222
6305	24-X--1.996	1A.STAFE BTA 07-XI--1.996	NO.561.207
6929	25-XI-1.996	1A.STAFE BTA 12-XII-1.996	NO.565.961
787	19-II-1.997	1A.STAFE BTA 25-II -1.997	NO.575.141
1024	28-II-1.997	1A.STAFE BTA 31-III-1.997	NO.579.245

CERTIFICA:

REFORMAS:

E.P. NO.	FECHA	NOTARIA	CIUDAD	FECHA	NO. INSC.
0007110	1997/10/28	0001	BOGOTA D.C.	1997/11/06	00609204
0001896	1998/03/16	0001	BOGOTA D.C.	1998/04/01	00628368
0002924	1998/04/21	0001	BOGOTA D.C.	1998/05/18	00634309
0002377	2000/06/14	0001	BOGOTA D.C.	2000/06/20	00733626
0000SIN	2004/06/22	0000	BOGOTA D.C.	2004/06/28	00940785
117	2010/04/30	0000	BOGOTA D.C.	2010/06/10	01390261
120	2010/08/18	0000	BOGOTA D.C.	2010/08/26	01409241
120	2010/08/30	0000	BOGOTA D.C.	2010/09/13	01413659
120	2010/07/29	0000	BOGOTA D.C.	2010/11/19	01429837
139	2011/06/07	0000	BOGOTA D.C.	2011/06/20	01489422
146	2011/10/24	0000	BOGOTA D.C.	2011/11/30	01531828

CERTIFICA:

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 27 DE JULIO DE 2040

CERTIFICA:

OBJETO SOCIAL: EL OBJETO DE LA SOCIEDAD ES EL EJERCICIO DE TODAS LAS ACTIVIDADES COMERCIALES PARA: 1) LA IMPORTACIÓN, EXPORTACIÓN, FABRICACIÓN, COMERCIALIZACIÓN, DISTRIBUCIÓN Y VENTA DE PRODUCTOS FARMACÉUTICOS, HIGIÉNICOS, VETERINARIOS E IMPLEMENTOS MÉDICOS. 2) CUALQUIER OTRA ACTIVIDAD LÍCITA DE COMERCIO RELACIONADA CON SU OBJETO SOCIAL PRINCIPAL Y TODO LO QUE SE RELACIONA CON LA IMPORTACIÓN DE LOS BIENES Y EQUIPOS NECESARIOS PARA EL DESARROLLO DE SU OBJETO SOCIAL. 3) TENER LA REPRESENTACIÓN EN COLOMBIA DE EMPRESAS O SOCIEDADES ESTABLECIDAS FUERA DEL TERRITORIO COLOMBIANO, CUYO OBJETO SEA SIMILAR O COMPLEMENTARIO. EN DESARROLLO DE SU OBJETO SOCIAL PRINCIPAL, LA SOCIEDAD PODRÁ ADELANTAR Y CELEBRAR LOS SIGUIENTES ACTOS Y CONTRATOS: A) EXPORTAR E IMPORTAR, AGENCIAR, DISTRIBUIR, COMERCIALIZAR, COMPRAR O VENDER A COMISIÓN O CONSIGNACIÓN O DE CUALQUIER OTRA FORMA O MODALIDAD, TODA CLASE DE EQUIPOS, APARATOS, BIENES AL POR MAYOR O AL DETAL, Y SERVICIOS RELACIONADOS CON SU ACTIVIDAD. B) GRAVAR EN CUALQUIER FORMA LOS BIENES DE SU PROPIEDAD MUEBLES O INMUEBLES, DAR EN PRENDA LOS PRIMEROS O HIPOTECAR LOS SEGUNDOS PARA GARANTIZAR OBLIGACIONES DE LA SOCIEDAD. C) CONSTITUIR APODERADOS QUE LE REPRESENTEN, ASOCIARSE CON OTRAS COMPAÑÍAS DE LA MISMA O PARECIDA NATURALEZA Y EN GENERAL REALIZAR TODA CLASE DE OPERACIONES COMERCIALES O CIVILES Y EJECUTAR O CELEBRAR TODA CLASE DE CONTRATOS O ACTOS DEL MISMO ORDEN, YA SEAN INDUSTRIALES, COMERCIALES O FINANCIEROS

ENCAMINADOS A ALCANZAR LOS FINES--QUE SE PROPONEN:--D) ADQUIRIR, ENAJENAR, ADMINISTRAR, RECIBIR O DAR EN ARRENDATARIO O A CUALQUIER TÍTULO, TODA CLASE DE BIENES MUEBLES E INMUEBLES. E) INTERVENIR ANTE TERCEROS O ANTE LOS ACCIONISTAS MISMOS COMO ACREEDORA O COMO DEUDORA EN TODA CLASE DE OPERACIONES DE CRÉDITO, DANDO O RECIBIENDO LAS GARANTÍAS DEL CASO, CUANDO HAYA LUGAR A ELLAS; F) EFECTUAR CUALQUIER CLASE DE OPERACIONES DE CRÉDITO ACTIVO O PASIVO, TALES COMO CONSTITUIR DEPÓSITOS, EFECTUAR PRESTAMOS. OTORGAR O RECIBIR DOCUMENTOS NEGOCIABLES, GIRAR, ACEPTAR, ENDOSAR, ASEGURAR Y NEGOCIAR EN GENERAL TÍTULOS VALORES RECIBIRLOS EN PAGO; G) CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCTENTES AL BUEN LOGRO DE LOS FINES SOCIALES.

CERTIFICA:

CAPITAL:

** CAPITAL AUTORIZADO **

VALOR : \$22,000,000,000.00
NO. DE ACCIONES : 22,000,000.00
VALOR NOMINAL : \$1,000.00

** CAPITAL SUSCRITO **

VALOR : \$20,877,288,000.00
NO. DE ACCIONES : 20,877,288.00
VALOR NOMINAL : \$1,000.00

** CAPITAL PAGADO **

VALOR : \$20,877,288,000.00
NO. DE ACCIONES : 20,877,288.00
VALOR NOMINAL : \$1,000.00

CERTIFICA:

REPRESENTACION LEGAL: LA SOCIEDAD CONTARÁ CON UN GERENTE, QUIEN TENDRÁ DOS SUPLENTE DENOMINADOS SUBGERENTES, QUIENES LO REEMPLAZARÁN EN LAS FALTAS OCASIONALES, TEMPORALES O ABSOLUTAS DE AQUEL.

CERTIFICA:

** NOMBRAMIENTOS **

QUE POR ACTA NO. 127 DE ASAMBLEA DE ACCIONISTAS DEL 12 DE NOVIEMBRE DE 2010, INSCRITA EL 23 DE NOVIEMBRE DE 2010 BAJO EL NUMERO 01430759 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

GERENTE

PALACIOS LUIS ALBERTO

C.E. 000000000319788

QUE POR ACTA NO. 117 DE ASAMBLEA DE ACCIONISTAS DEL 30 DE ABRIL DE 2010, INSCRITA EL 10 DE JUNIO DE 2010 BAJO EL NUMERO 01390261 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

SUBGERENTE

MUÑOZ MARTINEZ ORLANDO

C.C. 000000008317044

QUE POR ACTA NO. 139 DE ASAMBLEA DE ACCIONISTAS DEL 7 DE JUNIO DE 2011, INSCRITA EL 20 DE JUNIO DE 2011 BAJO EL NUMERO 01489425 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE

IDENTIFICACION

SUBGERENTE

PICART LAURENZ FRANCISCO JAVIER

C.E. 00000000E399661

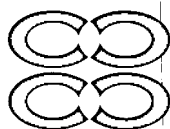
CERTIFICA:

FACULTADES DEL REPRESENTANTE LEGAL: EL GERENTE DE LA SOCIEDAD TIENE A



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**Cámara
de Comercio
de Bogotá**

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SU CARGO LA ADMINISTRACIÓN INMEDIATA DE LA SOCIEDAD, ASÍ COMO LA REPRESENTACIÓN LEGAL DE LA MISMA Y EN TAL VIRTUD LE ESTÁN ASIGNADAS LAS SIGUIENTES FUNCIONES Y ATRIBUCIONES: A) LLEVAR LA REPRESENTACIÓN DE LA ENTIDAD, TANTO JUDICIAL COMO EXTRAJUDICIALMENTE. B) EJECUTAR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS. C) CONSTITUIR, PARA CASOS ESPECIALES, APODERADOS JUDICIALES O EXTRAJUDICIALES. D) CELEBRAR LOS ACTOS, OPERACIONES Y CONTRATOS CONDUCENTES AL BUEN LOGRO DEL OBJETO DE LA SOCIEDAD. E) CUIDAR DE LA RECAUDACIÓN E INVERSIÓN DE LOS FONDOS DE LA SOCIEDAD. F) PRESENTAR A LA REUNIÓN ORDINARIA ANUAL DE LA ASAMBLEA GENERAL DE ACCIONISTAS, EL INVENTARIO Y LOS ESTADOS FINANCIEROS DE PROPÓSITO GENERAL DE FIN DE EJERCICIO, JUNTO CON UN INFORME ESCRITO RELACIONADO CON LA SITUACIÓN Y LA MARCHA DE LA ENTIDAD. G) CREAR LOS EMPLEADOS NECESARIOS PARA LA DEBIDA MARCHA DE LA SOCIEDAD, SEÑALAR SUS FUNCIONES Y ASIGNACIONES Y HACER LOS NOMBRAMIENTOS CORRESPONDIENTES. H) CONVOCAR A LA ASAMBLEA GENERAL CUANDO PROCEDA HACERLO CONFORME A LA LEY O A ESTOS ESTATUTOS. I) PRESENTAR A LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO ASÍ LO SOLICITE, ESTADOS FINANCIEROS MENSUALES DE PRUEBA E INFORMES. J) EJERCER LAS FUNCIONES QUE LE DELEGUE LA ASAMBLEA GENERAL DE ACCIONISTAS. K) CUMPLIR Y HACER QUE SE CUMPLAN EN OPORTUNIDAD Y DEBIDAMENTE TODAS LAS EXIGENCIAS DE LAS LEYES EN RELACIÓN CON EL FUNCIONAMIENTO Y LAS ACTIVIDADES DE LA INSTITUCIÓN. L) LAS DEMÁS QUE LE CORRESPONDAN CONFORME A LA LEY Y A ESTOS ESTATUTOS. EL GERENTE DE LA SOCIEDAD DEBERÁ CONTAR CON AUTORIZACIÓN PREVIA DE LA ASAMBLEA GENERAL DE ACCIONISTAS, CUANDO PRETENDA SUSCRIBIR EN NOMBRE DE LA SOCIEDAD (I) ACTOS O CONTRATOS PARA ADQUIRIR, ENAJENAR, RECIBIR O DAR EN ARRENDAMIENTO O A CUALQUIER OTRO TÍTULO, TODA CLASE DE BIENES INMUEBLES DE LA SOCIEDAD O BIENES MUEBLES DIFERENTES A LOS PRODUCTOS COMERCIALIZADOS ORDINARIAMENTE POR LA SOCIEDAD, ASÍ COMO (II) ACTOS O CONTRATOS, INDEPENDIENTE DE SU OBJETO, QUE SUPERE EN CUANTÍA EL EQUIVALENTE A 300 SMLMV (TRESCIENTOS SALARIOS MÍNIMOS MENSUALES LEGALES VIGENTES).

CERTIFICA:

QUE POR ESCRITURA PUBLICA NO. 3511 DE LA NOTARIA 18 DE BOGOTA D.C., DEL 8 DE SEPTIEMBRE DE 2010, INSCRITA EL 1 DE OCTUBRE DE 2010 BAJO EL NO. 00018604 DEL LIBRO V, COMPARECIO JOSE ANTONIO JAIME ESCOBAR IDENTIFICADO CON CEDULA DE CIUDADANÍA NO. 19.262.407 DE BOGOTA, EN SU CALIDAD DE GERENTE DE LABORATORIOS SYNTHESIS LTDA., POR MEDIO DE LA PRESENTE ESCRITURA PUBLICA, CONFIERE PODER GENERAL AL A OLGA VICTORIA PRIETO ZAMORA, IDENTIFICADA CON CEDULA DE CIUDADANÍA NO. 52.780.303 DE BOGOTA PARA QUE EN NOMBRE DE LA SOCIEDAD LABORATORIOS SYNTHESIS S.A.S., PROMUEVA Y DEFienda LOS INTERESES DE LA SOCIEDAD JUDICIAL Y EXTRAJUDICIALMENTE, EN TODA ESPECIE DE GESTIONES Y ACTUACIONES ANTE LAS AUTORIDADES ADMINISTRATIVAS O JURISDICCIONALES Y EN ESPECIAL PARA: A. DILIGENCIAR Y SUSCRIBIR LOS DOCUMENTOS NECESARIOS

PARA EL REGISTRO DE INVERSIONES EXTRANJERAS ANTE LAS AUTORIDADES COLOMBIANAS. B. TRANSIGIR, DESISTIR Y APELAR A DECISIONES DE ÁRBITROS O DE AMIGABLES COMPONEDORES EN LAS CUESTIONES EN QUE TENGA INTERÉS FRENTE A TERCEROS, A LOS ASOCIADOS MISMOS O A SUS ADMINISTRADORES. C. ADELANSTAR CUALQUIER TIPO DE TRÁMITE ANTE EL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES. D. RECIBIR NOTIFICACIÓN DE TODAS LAS PROVIDENCIAS QUE SE EXPIDAN DENTRO DE LOS DIFERENTES TRÁMITES E INTERPONER LOS RECURSOS PROPIOS DE LA VÍA GUBERNATIVA. E. REPRESENTAR Y VIGILAR ANTE LOS FUNCIONARIOS, OFICINAS Y DEPENDENCIAS DEL INSTITUTO DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA O A LA ENTIDAD QUE HAGA SUS VECES, TODAS LAS SOLICITUDES QUE CONTENGAN TRÁMITES A NOMBRE DE LABORATORIOS SYNTHESIS S.A.S. F. SOLICITAR, OBTENER, REVISAR Y MODIFICAR REGISTROS SANITARIOS. G. OBTENER ANTE LAS OFICINAS Y AUTORIDADES NACIONALES QUE CORRESPONDAN Y EN ESPECIAL DE LA DIVISIÓN DE PROPIEDAD INDUSTRIAL DE LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, REGISTROS DE MARCAS, RENOVACIÓN DE REGISTROS MARCARIOS, ANOTACIÓN DE TRASPASOS Y CAMBIO DE NOMBRE, PRESENTACIÓN Y TRÁMITE DE OPOSICIONES, PRESENTACIÓN Y TRÁMITE DE RECURSOS POR LA VÍA GUBERNATIVA Y DEMÁS DILIGENCIAS RELACIONADAS, A CUYO EFECTO LA FACULTA PARA DAR ANTE DICHAS AUTORIDADES, PARA ELEVAR SOLICITUDES, FORMULAR DESCRIPCIONES, APELACIONES Y RECLAMOS, SOLICITAR TESTIMONIO, RECIBIR, DESISTIR, SUSTITUIR, CANCELAR, TRANSIGIR, RENUNCIAR, ACEPTAR NOTIFICACIONES Y NOMBRAR APODERADOS JUDICIALES Y EXTRAJUDICIALES. H. ADQUIRIR MARCAS, PATENTES, PROCEDIMIENTOS DE FABRICACIÓN, EXPLOTADAS EN CUALQUIER FORMA, YA SEA UTILIZÁNDOLOS DIRECTAMENTE O PERMITIENDO SU EXPLOTACIÓN POR OTRAS PERSONAS NATURALES O JURÍDICAS CONTRA EL PAGO DE REGALÍAS O PARTICIPACIONES. I. CELEBRAR Y EJECUTAR EN GENERAL TODOS LOS ACTOS Y CONTRATOS PREPARATORIOS, COMPLEMENTARIOS O ACCESORIOS DE TODOS LOS ANTERIORES, LOS QUE SE RELACIONEN CON LA EXISTENCIA Y FUNCIONAMIENTO DE LA SOCIEDAD, Y LOS QUE SEAN CONDUCTENTES AL BUEN LOGRO DE LOS FINES SOCIALES. J. RECIBIR NOTIFICACIONES DE CUALESQUIERA TIPO DE ACTOS EMANADOS DE LAS AUTORIDADES ADMINISTRATIVAS O JUDICIALES. K. PRESENTAR RECURSOS POR LA VÍA ADMINISTRATIVA O JUDICIAL, RENUNCIAR A TÉRMINOS, DESISTIR, CONCILIAR, TRANSIGIR Y MODIFICAR. L. ELEVAR PETICIONES Y SOLICITAR INFORMACIÓN A LAS AUTORIDADES ADMINISTRATIVAS Y JURISDICCIONALES. M. PRESENTAR DEMANDAS ANTE LAS AUTORIDADES ADMINISTRATIVAS Y JUDICIALES. N. SUSTITUIR EL PRESENTE PODER Y REVOCAR TAL SUSTITUCIÓN DENTRO DE LA REPÚBLICA DE COLOMBIA.

CERTIFICA:

**** REVISOR FISCAL ****

QUE POR DOCUMENTO PRIVADO DE REVISOR FISCAL DEL 13 DE JUNIO DE 2012, INSCRITA EL 16 DE JUNIO DE 2012 BAJO EL NUMERO 01643111 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PRINCIPAL	
MATTA DE ANTONIO LILIBETH ZULEYM	C.C. 000001030529287
REVISOR FISCAL SUPLENTE	
MOYA CHAVES ANDREA PATRICIA	C.C. 000000052774031

QUE POR ACTA NO. 119 DE ASAMBLEA DE ACCIONISTAS DEL 22 DE JUNIO DE 2010, INSCRITA EL 8 DE JULIO DE 2010 BAJO EL NUMERO 01397026 DEL LIBRO IX, FUE (RON) NOMBRADO (S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL PERSONA JURIDICA	
DELOITTE & TOUCHE LTDA	N.I.T. 000008600058134

CERTIFICA:



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PERMISO DE FUNCIONAMIENTO:QUE POR RESOLUCION NO.05952 DEL 11 DE - JUNIO DE 1.985, INSCRITA EN ESTA CAMARA DE COMERCIO EL 8 DE JULIO DE 1.985 BAJO EL NO. 172.879 DEL LIBRO IX, LA SUPERINTENDENCIA - DE SOCIEDADES CONCEDIO PERMISO DEFINITIVO DE FUNCIONAMIENTO A LA SOCIEDAD.

CERTIFICA:

QUE POR RESOLUCION NO.09006 DEL 19 DE DICIEMBRE DE 1.986 SUPERIN- TENDENCIA DE SOCIEDADES INSCRITA EL 16 DE ENERO DE 1.987 BAJO EL NO.204.133 DEL LIBRO IX, SE AUTORIZO A LA SOCIEDAD PARA COLOCAR SETENTA Y CUATRO MIL (\$74.000) ACCIONES DE LAS QUE TIENE EN RE- SERVA, A SU VALOR NOMINAL DE CIEN PESOS (\$100.00) M/CTE., CADA UNA.

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 28 DE JUNIO DE 2011, INSCRITO EL 1 DE JULIO DE 2011 BAJO EL NUMERO 01492789 DEL LIBRO IX, SE COMUNICO QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL POR PARTE DE LA SOCIEDAD MATRIZ: LABORATORIOS SYNTHESIS S A S, RESPECTO DE LAS SIGUIENTES SOCIEDADES SUBORDINADAS:

- SOCIEDAD PARA LA ENSEÑANZA DE LA HOMEOPATIA CLINICA S A S QUIEN SE IDENTIFICARA CON LA SIGLA S E C H

DOMICILIO: BOGOTA D.C.

FECHA DE CONFIGURACION DE LA SITUACION DE CONTROL : 2011-05-31

CERTIFICA:

QUE POR DOCUMENTO PRIVADO DE REPRESENTANTE LEGAL DEL 9 DE MARZO DE 2011, INSCRITO EL 18 DE MARZO DE 2011 BAJO EL NUMERO 01462396 DEL LIBRO IX, COMUNICO LA SOCIEDAD MATRIZ:

- EUROPEAN CHEMICALS & CO

DOMICILIO: (FUERA DEL PAIS)

QUE SE HA CONFIGURADO UNA SITUACION DE CONTROL CON LA SOCIEDAD DE LA REFERENCIA.

CERTIFICA:

*** ACLARACIÓN SITUACIÓN DE CONTROL Y DE GRUPO EMPRESARIAL ***
SE ACLARA LA SITUACIÓN DE CONTROL Y GRUPO EMPRESARIAL INSCRITA CON EL NO. 01462396 DEL 9 DE MARZO DE 2011 DEL LIBRO IX EN EL SENTIDO DE INDICAR QUE SE CONFIGURÓ DESDE EL 19 DE NOVIEMBRE DE 2010.

CERTIFICA:

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS:

NOMBRE: CARDIOPHARM

MATRICULA NO: 00537358 DE 3 DE MARZO DE 1993

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : GENERICS

MATRICULA NO : 00664623 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : MASCOTT

MATRICULA NO : 00664622 DE 18 DE SEPTIEMBRE DE 1995

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : ONCOPHARM

MATRICULA NO : 00625764 DE 13 DE DICIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : GASTROPHARM

MATRICULA NO : 00621442 DE 2 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : GYNECOPHARM

MATRICULA NO : 00621245 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : ENTEROPHARM

MATRICULA NO : 00621244 DE 1 DE NOVIEMBRE DE 1994

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

NOMBRE : EQUIPHARMA

MATRICULA NO : 00556630 DE 21 DE JULIO DE 1993

RENOVACION DE LA MATRICULA : EL 29 DE FEBRERO DE 2012

ULTIMO AÑO RENOVADO : 2012

CERTIFICA:

DE CONFORMIDAD CON LO ESTABLECIDO EN EL CODIGO DE PROCEDIMIENTO ADMINISTRATIVO Y DE LO CONTENCIOSO Y DE LA LEY 962 DE 2005, LOS ACTOS ADMINISTRATIVOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME DIEZ (10) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS.

* * * EL PRESENTE CERTIFICADO NO CONSTITUYE PERMISO DE * * *
* * * FUNCIONAMIENTO EN NINGUN CASO * * *

SEÑOR EMPRESARIO, SI SU EMPRESA TIENE ACTIVOS INFERIORES A 30.000 SMLMV Y UNA PLANTA DE PERSONAL DE MENOS DE 200 TRABAJADORES, USTED TIENE DERECHO A RECIBIR UN DESCUENTO EN EL PAGO DE LOS PARAFISCALES DE 75% EN EL PRIMER AÑO DE CONSTITUCION DE SU EMPRESA, DE 50% EN EL SEGUNDO AÑO Y DE 25% EN EL TERCER AÑO. LEY 590 DE 2000 Y DECRETO 525 DE 2009.

RECUERDE INGRESAR A www.supersociedades.gov.co PARA VERIFICAR SI SU EMPRESA ESTA OBLIGADA A REMITIR ESTADOS FINANCIEROS. EVITE SANCIONES.

EL SECRETARIO DE LA CAMARA DE COMERCIO,



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VALOR : \$ 4,000

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES

