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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: COMPOSICION FARMACEUTICA ESTABLE Y METODOS PARA UTILIZAR LA MISMA.

Gaceta: 647 de 29 de junio de 2012, No. de publicación 838

2. Datos del Opositor

☐ Persona Natural

☒ Persona Jurídica

TECNOQUIMICAS S.A.

Nombre o denominación / Razón social completa

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

Número 890 300 466-5

Dirección Calle 23 No. 7-39 , Ciudad Cali

Teléfono (092) 882.55.55 Fax: (092) 883.88.59 E-mail: _____



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:

REYES VILLAMIZAR JOSE LUIS

79 152.473

44655

Apellidos y Nombre

Documento de identificación

T.P. No.

Dirección del representante

Cra 17 No. 88-23 Of.205

Dirección electrónica

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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

6. Fundamentos de la oposición

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

Justificación: VER ANEXO

Prórroga:

SI

☒

NO

☐

7. Anexos

☒

Comprobante de pago de la tasa para la presentación de la solicitud No. _____ Fecha: _____

☒

Poder, si fuera el caso con el que se acredita la representación.

☒

Pruebas de los fundamentos de la oposición

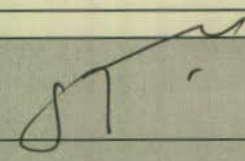
☒

Copias para traslado 12 Folios

8. Firma

JOSÉ LUIS REYES VILLAMIZAR

Nombre y apellidos


Firma

79.152.473

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44655

T.P.

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: Expediente 11-163-902

TÍTULO SOLICITADO: Composición farmacéutica estable y métodos para utilizar la misma.

PUBLICACIÓN: Gaceta 647 de 29/06/2012, N° de publicación 838.

PRIORIDAD: US 61/173.763 de 29/04/2009

SOLICITANTE: AMARIN PHARMA, INC

APODERADO: LUZ CLEMENCIA DE PAEZ.

TRÁMITE: PRESENTACION DE OPOSICION

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUIMICAS S.A.**, en ejercicio de lo dispuesto por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Negar el beneficio patentario a la solicitud contenida en el expediente **11-163-902**, por no cumplir con los requisitos de patentabilidad a que se refieren los artículos 14, 16, 18 y 20d de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos de hecho y de derecho que me permito exponer a continuación.

II. LEGÍTIMO INTERÉS

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

III. FUNDAMENTOS DE LA OPOSICION

La solicitud colombiana en trámite **11-163-902** referida 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 5Meq/kg y después de almacenamiento a 25°C y 60% de HR durante un periodo de 6 meses la composición tiene un segundo valor de peróxido no mayor de 8Meq/kg, y que además comprende un método de tratamiento o prevención de una enfermedad cardiovascular, no reúne los requisitos necesarios para otorgársele el privilegio de patente de invención, como se demuestra a través de los siguientes argumentos:

En primer lugar, es necesario resaltar que el capítulo reivindicatorio de la solicitud colombiana en curso, específicamente en sus reivindicaciones 44 a 46 se encuentra dirigido a métodos de tratamiento, lo cual es inaceptable a la luz de la Decisión 486.

Sin perjuicio de lo anterior me permito hacer notar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y aplicación Industrial, siendo éste último de imposible cumplimiento en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías es del resorte de la profesión médica y no de las actividades industriales.

En otro aspecto, y esta vez refiriéndonos a la novedad y nivel inventivo de la solicitud colombiana en trámite, existen diversos documentos que revelan con anterioridad composiciones con EPA o etil-EPA para ser administrados en forma de medicamentos encapsulados, tableteados o en forma de alimentos, siendo estables al medio ambiente (es importante tener en cuenta la susceptibilidad de degradación del ácido eicosapentanoico) e incluso con estabilidad mejorada tal como ocurre en la presente solicitud colombiana en trámite, por tanto la composición reivindicada no es nueva pues ya se conocía con anterioridad, tal y como lo expone la publicación US 2006/0134178, veamos:

Composition containing organic substance having double bond with improved oxidative stability

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.

En este documento claramente se evidencia que en la práctica farmacéutica, es común realizar composiciones farmacéuticas con ácidos grasos poliinsaturados o EPA como ingredientes activos, los cuales son más susceptibles a degradación que los ésteres, lo que demuestra que la inclusión de este tipo de compuestos es ampliamente reconocida en el estado de la técnica, así como lo es la inclusión de antioxidantes en dichas composiciones, en este caso la inclusión de tocoferol-, lo que demuestra que lo revelado en la solicitud colombiana en trámite ya había sido descrito en el estado del arte.

Si tenemos en cuenta que la reivindicación independiente 1 de la solicitud colombiana en trámite pretende proteger lo siguiente:

1) 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.

Vemos que lo contenido en ella no es nuevo ya que dicha composición se revelaba previamente en la publicación US 2006/0134178 antes mencionada, así

mismo y teniendo en cuenta lo anterior, tampoco podrían ser nuevas las reivindicaciones dependientes 2 – 43, veamos:

CARACTERÍSTICAS DE LA REIVINDICACION 1 CO 11-163-902		US 2006/0134178	
Composición		Pág 8 Reivindicación 4	
Comprende EPA		Pág 8 [0119] Pág 8 Reivindicación 4	
En una cápsula		Pág 5 [0054]	
Aceptable Estabilidad en el tiempo		Abstract Pág 2 [0016]	

(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.

[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.

(...)

powder base material in the same manner. If the composition is added to food, it is determined whether the composition is in oil or fat form or powdered oil form, depending on the characteristics of the food. The composition may be added to general food, or encapsulated or tableted to prepare health food or a supplement.

(pág 5)

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.

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

Como se observa a simple vista, la composición de la reivindicación 1 no es nueva ya que no hay características esenciales que la diferencien de las enseñanzas divulgadas en la publicación US 2006/0134178.

Adicionalmente, la anterioridad mencionada sugiere adicionar (página 2 párrafo [0019] (13)) un antioxidante el cual puede ser tocoferol tal y como se reivindica en la solicitud colombiana en trámite (reivindicaciones 7 y 8).

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

Por lo tanto al utilizar éste componente tampoco podría conferírsele novedad y/o nivel inventivo a la solicitud ya que cualquier experto medianamente versado en la materia utilizaría los conocimientos enseñados por éste único documento para lograr lo reivindicado a lo largo de todo el capítulo reivindicatorio en trámite y así conseguir de igual forma los efectos técnicos logrados por la solicitud en lo concerniente a estabilidades mejoradas, perfiles de disolución y biodisponibilidad de la composición.

Adicional al anterior documento se encuentran también otras publicaciones donde se muestra con exactitud ejemplos de formulaciones que contienen EPA y/o DHA, con sus proporciones y cantidades a usar, veamos por ejemplo la publicación **US 2003/0100610 "Use of polyunsaturated fatty acids for the primary prevention of major cardiovascular events"**.

En este documento, claramente se evidencia que la práctica de elaborar composiciones farmacéuticas con ácidos grasos poliinsaturados, EPA y/o DHA como ingredientes activos en eventos cardiovasculares tal y como lo reivindica la solicitud colombiana en cuestión, era ampliamente reconocida en el estado de la técnica y además sugiere de forma puntual las formulaciones que pueden realizarse incluso con antioxidantes como el tocoferol dentro de las mismas:

página 2 [0025]

	A ¹	B ¹	C ¹	D ¹	E ¹	F ¹	G ¹	H ²	I ³
EPA	>40	>44	>40	>25	>80	>20	<15	>40	>40
DHA	>34	>30	>34	>20	<10	>25	>80	>30	>30
EPA + DHA	>85	>80	>80	>50	>80	>50	>85	>80	>80
esters ⁴		>3	—						
tot.esters ⁵			>90						
α-tocopherol	0.03	0.03	0.1	0.3	0.1	0.3	0.03	0.1	0.1

1-ethyl esters; 2-acids; 3-sodium salts; 4-ethyl esters of other (C₂₀, C₂₁, C₂₂) ω-3 acids;
5-total ethyl esters of ω-3 acids.

página 3 [0026]

	A (mg)	B (mg)	C (mg)
EPA ¹	525	—	>400
DHA ¹	315	—	>340
EPA + DHA		850	>800
Total ω-3 ¹		—	>900
d-α-tocopherol	4 I.U.	—	4 I.U.
d,l-α-tocopherol		0.3	
gelatin	246	—	246
gelatin succinate		233	
glycerol	118	67	118
OFR	2.27	—	2.27
OFG	1.27		1.27
SOB		1.09	
SPOB		0.54	

1-ethyl esters; OFR: red iron oxide OFG: yellow iron oxide; SOB: sodium p-oxybenzoate;
SPOB: sodium propyl p-oxybenzoate; I.U.: international units.

De ésta forma se comprueba una vez más que la composición no es nueva pues ya había sido desarrollada anteriormente con las mismas características que la

composición de la solicitud colombiana en trámite y consiguiendo la solución al mismo problema técnico.

Por si no fuese suficiente la información expuesta anteriormente, también se puede demostrar que utilizar materiales que forman películas y agentes plastificantes en el material de encapsulado es una práctica común, tal y como se expone en la publicación US 2003/0104048 **“Pharmaceutical dosage forms for highly hydrophilic materials”**:

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.

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.

[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.

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.

[0057] Among the preferred triglycerides, more preferred triglycerides include: coconut oil; corn oil; olive oil; palm oil; peanut oil; safflower oil; sesame oil; soybean oil; hydrogenated castor oil; hydrogenated coconut oil; partially hydrogenated soybean oil; glyceryl tricaprate; glyceryl trilaurate; glyceryl trioleate; glyceryl trilinoleate; glyceryl tricaprylate/caprate; glyceryl tricaprylate/caprate/laurate; glyceryl tricaprylate/caprate/linoleate; glyceryl tricaprylate/caprate/stearate; saturated polyglycolized glycerides (Gelucire 44/14, Gelucire 14 50/13 and Gelucire 53/10); linoleic glycerides (Maisine 35-I); and caprylic/capric glycerides (Imwitor 742).

En dicha publicación (US 2003/0104048) inclusive se revelan con exactitud cuáles plastificantes higroscópicos pueden emplearse, entre los que se menciona glicerol tal y como se describe en la reivindicación 17 de la solicitud colombiana en trámite. De igual manera, se revelan materiales formadores de película como la gelatina tal como se describe en la reivindicación 18 de la solicitud colombiana, y de la misma forma se describen plastificantes no higroscópicos como los que se pretenden proteger en las reivindicaciones 24 y 25 de la solicitud colombiana, es decir, maltitol, lactitol, xilitol, hidrolizado de almidón hidrogenado y jarabe de glucosa.

En conclusión la solicitud colombiana en trámite incumple los requisitos fundamentales para otorgársele el privilegio de patente de invención si se tiene en cuenta que, pretende atribuirse exclusividad sobre un "método de tratamiento"; porque su composición tal y como se reivindica carece totalmente de novedad, lo cual ha quedado demostrado no solo por uno sino por dos documentos que revelan específicamente la misma formulación; porque el hecho de adicionar antioxidantes como el tocoferol para ayudar a la estabilidad de las composiciones como se reivindica posteriormente, ya era una práctica conocida y se evidencia en los mismos documentos, los cuales sin más, anulan la novedad de la solicitud en trámite y por último, porque utilizar materiales que forman películas y agentes

plastificantes para lograr el encapsulado se encontraba también en el estado de la técnica. Así mismo, la solicitud en trámite carece también de nivel inventivo puesto que todos los componentes reivindicados ya se encontraban descritos con anterioridad en el estado de la técnica, por lo cual, una persona medianamente conocedora de la materia combinando los documentos aquí expuestos o incluso sin combinarlos llegaría fácilmente a lo que se pretende proteger y conseguiría de forma directa el efecto técnico, es decir, una estabilidad adecuada para las composiciones reivindicadas.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que su despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18 y 20 literal d de (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La Publicación Americana US 20060134178 "Composition containing organic substance having double bond with improved oxidative stability" págs. 2, 5, 8 y abstract.
- La Publicación Americana US 20030100610 "use of polyunsaturated fatty acids for the primary prevention of major cardiovascular events" págs. 2 y 3.
- La Publicación Americana US 20030104048 "Pharmaceutical dosage forms for highly hydrophilic materials" pág 3, abstract.

VI. ANEXOS

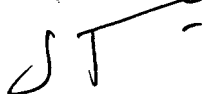
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos

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

VII. NOTIFICACIONES

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

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79'152.473 de Usaquén

T.P.A. 44.655 del C.S.J.



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**

(76) **Inventors: Nobushige Doisaki, Tokyo (JP);
Tsuyoshi Koriyama, Tokyo (JP); Jun
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(21) **Appl. No.: 10/535,413**
(22) **PCT Filed: Nov. 21, 2003**
(86) **PCT No.: PCT/JP03/14877**

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Publication Classification
(51) **Int. Cl.**
A61K 47/00 (2006.01)
A61K 35/60 (2006.01)
(52) **U.S. Cl. 424/439; 424/523**

(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.

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 fish oil.

[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, pinoresinol, epihinoresinol, syringaresinol, samine, sesamolinal, 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 or fat in Example 1.

fatty acid ester is used under conditions not allowing natural diffusion, preferably, it is finely powdered and uniformly dispersed.

[0052] In addition to the antioxidative sesame component and the ascorbic acid or ascorbyl fatty acid ester, a tocopherol may be added. The tocopherol may be selected from among α -, β -, γ -, and δ -tocopherols and mixed tocopherol, but preferably δ -tocopherol is used. Tocopherol is often added to commercially available polyunsaturated fatty acids and their salts and esters, such as refined fish oil, in the stage of production. Hence, use of these raw materials naturally results in a product containing tocopherol. Whether tocopherol is present or absent does not affect the synergistic effect of the antioxidative sesame component and the ascorbic acid or ascorbyl fatty acid ester.

[0053] The oil or fat whose oxidative stability has been enhanced by adding an antioxidative sesame component and ascorbic acid or an ascorbyl fatty acid ester can exhibit satisfactory oxidative stability alone, but it may be used in combination with another antioxidant. Also, it may be mixed with another oil or fat having superior oxidative stability (for example, vegetable oil). Other antioxidants include erythorbic acid, sodium erythorbate, isopropyl citrate, dibutylhydroxytoluene (BHT), and butylhydroxyanisole (BHA). Antioxidants used in combination in food include: food additives, such as tocopherols, hollyhock flower extract, Azuki extract, *aspergillus terreus* extract, calcium disodium ethylenediaminetetraacetate, disodium ethylenediaminetetraacetate, ellagic acid, erythorbic acid, sodium erythorbate, enju extract, γ -oryzanol, catechin, licorice oil extract, guajac resin, quercetin, isopropyl citrate, clove extract, enzymatically modified isouercitrin, enzymatically modified rutin (extract), enzymatically decomposed apple extract, sesame seed oil unsaponifiable matter, rice bran oil extract, enzymatically decomposed rice bran, L-cysteine hydrochloride, dibutylhydroxytoluene, Queensland arrowroot extract, essential oil-removed fennel extract, horseradish extract, sesamoline, sage extract, dropwort extract, buckwheat extract, amino acid-sugar reaction product, tea extract, tempeh extract, dokudami extract, rape seed oil extract, coffee bean extract, nordihydroguajaretic acid, sunflower seed extract, pimento extract, ferulic acid, butylhydroxyanisole, grape seed extract, blueberry leaf extract, propolis extract, hego-ginkgo leaf extract, hesperetin, pepper extract, garden balsam extract, gallic acid, propyl gallate, melaleuca oil, morin, chinese bayberry extract, eucalyptus leaf extract, gentian root extract, enzymatically decomposed rutin, rutin (extract), and rosemary extract; and antioxidants approved in other countries, such as thiodipropionic acid, distearyl thiodipropionate, octyl gallate, dodecyl gallate, and tert-butylhydroquinone.

[0054] Since the composition of the present invention has superior oxidative stability, it can be added to various types of food. For example, skimmed milk, milk cascain, milk protein, lactose, oligosaccharide, cane sugar, or dextrin is dissolved in hot water to mix, and then vitamins and minerals are dissolved in the water phase. The oil or fat of the present invention is added to the water phase and mixed with a homo-mixer or the like, followed by homogenizing with a homogenizer. The resulting emulsion is sterilized, concentrated, or spray-dried in the usual manner to yield modified powder milk. Also, the composition of the present invention may be powdered oil using various types of

powder base material in the same manner. If the composition is added to food, it is determined whether the composition is in oil or fat form or powdered oil form, depending on the characteristics of the food. The composition may be added to general food, or encapsulated or tableted to prepare health food or a supplement.

EXAMPLES

[0055] The present invention will be further described with reference to the following examples, but the invention is not limited to the examples.

[0056] In the examples, the following materials were used as the refined fish oil, sesamol, ascorbyl palmitate, ascorbic acid, δ -tocopherol.

[0057] Refined fish oil (containing 0.5% by weight of δ -tocopherol): DD Oil Type 3 (refined fish oil produced by refining tuna oil to a peroxide value of 5 meq/kg or less, an acid value of 1 or less, and a color Gardner of 3 or less by degumming, deacidification, deodorization, or other process), produced by Nippon Suisan Kaisha, Ltd.

[0058] Refined fish oil (not containing δ -tocopherol): taken as a sample before adding δ -tocopherol in the process of DD Oil Type 3 preparation, produced by Nippon Suisan Kaisha, Ltd.

[0059] Refined fish oil (sardine oil): DD Oil Type 2 (refined fish oil produced by refining sardine oil to a peroxide value of 5 meq/kg or less, an acid value of 1 or less, and a color Gardner of 3 or less by degumming, deacidification, deodorization, or other process; containing 28% by weight of EPA, 12% by weight of DHA, and 0.5% by weight of δ -tocopherol), produced by Nippon Suisan Kaisha, Ltd.

[0060] Sesamol: sesamol (purity: 98%) produced by Nacalai Tesque, Inc.

[0061] Ascorbyl palmitate: ascorbyl palmitate (purity: 95% or more) produced by Sankyo Foods Co. Ltd.

[0062] Ascorbic acid: L-(+)-ascorbic acid (purity: 99.5%) produced by Nacalai Tesque, Inc.

[0063] δ -Tocopherol: D- δ -tocopherol (purity: 90%) produced by Wako Pure Chemical Industries Eicosapentaenoic acid ethyl ester: prepared by ethanolysis of sardine oil in the presence of metallic sodium to prepare sardine oil ethyl ester and purifying the ester by distillation and HPLC to a purity of 99%.

[0064] α -Tocopherol: ($\pm$)- α -tocopherol (purity: 98%) produced by Wako Pure Chemical Industries

Example 1

<Test for Effect of Sesamol+Ascorbyl Palmitate+ δ -Tocopherol>

[0065] The following antioxidant preparations were added separately to refined fish oil (containing 0.5% by weight of δ -tocopherol) to prepare samples.

[0066] sesamol (1.0% by weight)+ascorbyl palmitate (0.01% by weight)

[0067] sesamol (1.0% by weight) alone

[0068] ascorbyl palmitate (0.01% by weight) alone

[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 stored at 37° C. The oxygen concentration in the headspace

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 polyunsaturated fatty acid or its salt or ester.

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

5. A composition according to claim 3, 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 claim 3, wherein the ester of the polyunsaturated 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 the group consisting of sesamol, sesaminol, episesaminol,



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17

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(54) **USE OF POLYUNSATURATED FATTY ACIDS
FOR THE PRIMARY PREVENTION OF
MAJOR CARDIOVASCULAR EVENTS**

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(57) **ABSTRACT**

The use of polyunsaturated fatty acids of the ω -3 series such as eicosapentaenoic acid (EPA, C_{20:5} ω -3), docosahexaenoic acid (DHA, C_{22:6} ω -3), or their pharmaceutically acceptable derivatives is described for the primary prevention of major cardiovascular events in subjects who have not undergone previous infarct episodes.

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USE OF POLYUNSATURATED FATTY ACIDS FOR THE PRIMARY PREVENTION OF MAJOR CARDIOVASCULAR EVENTS

[0001] The invention relates to the use of polyunsaturated fatty acids for the primary prevention of major cardiovascular events.

[0002] In particular, the invention concerns the use of polyunsaturated fatty acids of the ω -3 series such as eicosapentaenoic acid (EPA, $C_{20:5}$ ω -3), docosahexaenoic acid (DHA, $C_{22:6}$ ω -3), or their pharmaceutically acceptable derivatives, either alone or mixed together, for the primary prevention of major cardiovascular events.

[0003] The beneficial effects of polyunsaturated fatty acids of the ω -3 series on multiple risk factors for cardiovascular illnesses are well known; for example the patents IT 1235879, U.S. Pat. No. 5,502,077, U.S. Pat. No. 5,656,667 and U.S. Pat. No. 5,698,594 refer respectively to hypertriglyceridemia, defects of the cholesterol level and hypertension. However, each of the cited documents deal with the treatment of risk factors, not with real and proclaimed illnesses.

[0004] U.S. Pat. No. 5,753,703 describes the use of L-carnitine or its derivatives in association with polyunsaturated fatty acids of the ω -3 series or their esters, in particular EPA and DHA, for the prevention and treatment of cardiovascular disorders, vascular pathologies, diabetic peripheral neuropathies, and atherosclerotic, thromboembolytic and tissue disorders.

[0005] EP-B-0409903 describes a process for preparing high concentration mixtures of EPA and DHA and/or their esters useful for treating hyperlipemia and related pathologies, thrombosis, cardiac infarct, platelet aggregation, as anticoagulants in the prevention of atherosclerosis, for the treatment of cerebral infarct, of lesions and occlusions caused by vasomotor spasms, of diabetes and its complications, of chronic and acute inflammations, of autoimmune symptoms, in the prevention of side effects caused by non-steroid anti-inflammatories at the gastrointestinal level and in tumour prevention.

[0006] CN 1082909 describes compositions based on ethyl esters of EPA and DHA and other polyunsaturated fatty acids of the ω -3 series in association with soya phospholipids, oenothera odorata and ginkgetin, as antithrombotic and antidementia agents for treating for example dementia and infarct of the myocardium.

[0007] U.S. Pat. No. 5,760,081 describes a method for preventing imminent fibrillation of the myocardial ventricle by intravenous infusion of a composition containing EPA, where the subject at risk of imminent fibrillation has already often been the protagonist of an episode of infarct of the myocardium and where the infusion is effected within 3 hours of the infarct episode, possibly using intracardiac injection. These are always situations of extreme emergency and of parenteral intervention, for the specific treatment of ventricular fibrillation.

[0008] Swann et al., Clinical Drug Investigation 15 (6), 473, 1998 have also shown that the administration of EPA and DHA ethylesters, at a dose of 4 g per day, leads to a decrease in triglycerides and total apolipoprotein C III and to an increase in antithrombin III, in subjects-with abnormal plasmatic lipoprotein symptoms and have undergone an infarct of the myocardium, they having consequently suggested that an administration of these compositions can

result in an improvement in the lipoprotein level and hence a decrease in the relative risk factors.

[0009] WO 00/48592 describes the use of a mixture of EPA and DHA ethylesters in quantities greater than 25 wt. % for preventing death, in particular "sudden death" in patients who have already suffered an infarct of the myocardium. This therefore represents the use of said mixture in so-called secondary death prevention, i.e. in subjects who have already suffered infarct.

[0010] The prevention of cardiovascular damage by means of fatty acid mixtures described in the state of the art is therefore focused on "secondary" prevention of cardiovascular damage, i.e. aimed at protecting a subject who has already suffered an infarct, whereas "primary" prevention of major cardiovascular events, i.e. prevention in subjects who, while affected by various pathologies of the cardiocirculatory and/or cardiorespiratory systems, have not yet suffered an infarct episode, constitutes a technical problem which is still felt in this sector.

[0011] According to a first aspect the invention relates to the use of polyunsaturated fatty acids of the ω -3 series for the preparation of a drug useful in the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, wherein the fatty acids comprise eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) and/or at least one pharmaceutically acceptable derivative thereof, in quantities greater than or equal to 25 wt % on the total fatty acid weight.

[0012] In the present description, the expression "polyunsaturated fatty acids of the ω -3 series" means those long-chain polyunsaturated fatty acids, generally C_{16} - C_{24} , containing fish oils, in particular those having a C_{20} - C_{22} chain, which are predominant in purification processes.

[0013] The expression "major cardiovascular event" means in particular those events which involve reversible or irreversible cardiovascular damage, such as infarct of the myocardium and of individual coronary branches, death from cardiac causes, sudden death, etc., besides to infarct, broadly speaking, ictus etc., and those conditions prodromal to such major events, such as myocardial fibrillation, atrial and/or ventricular fibrillation, etc. Said major cardiovascular events are usually induced by various cardiocirculatory and cardiorespiratory pathologies such as coronary ischemic illness not displayed by previous infarct episodes, and by serious hypoxic/anoxic states caused by a sudden lack of oxygen (for example during anesthesia, surgery, etc.), possibly in the presence of conditions which contemplate an increase in the oxygen requirement (accentuated physical stress, drug abuse, acute hypertensive crises, etc.) and analogous acute and chronic pathologies due to cardiac defects of electrical and/or mechanical type.

[0014] The subjects affected by pathologies of the cardiocirculatory and cardiorespiratory system, hence not simply at prospective risk due to hypertriglyceridemia, hypertension or other, are representative of subjects definable at various levels as cardiopaths, by being affected, for example, by coronary ischemia detectable by coronarography, scintigraphy of the myocardium, electrocardiogram (ECG) under stress, etc., against which interventions of revascularization (angioplasty) or other possible pharmacological or invasive treatments have been proposed, and of subjects affected by electrical hyperexcitability of the myocardium cells, disorder of the diffusion of electrical excitement or of electrical conduction (arrhythmia, fibrillation, etc.) or by

other defects of mechanical type (cardiac insufficiency, decompensation), possibly aggravated by concomitant pathologies such as diabetes.

[0015] The use of polyunsaturated fatty acids of the ω -3 series according to the invention is particularly indicated if the occurrence of a major event is predicted, such as an infarct, in particular of the myocardium, death from a cardiological cause, or sudden death, and where such an occurrence takes place in cardiopathic subjects affected, for example, by coronary ischemia, arrhythmia, atrial and/or ventricular fibrillation, electrical hyperexcitability of the myocardium cells, disorder of the diffusion of electrical excitement or of electrical conduction of the myocardium, or cardiac disorders of mechanical type, for example cardiac insufficiency or cardiac decompensation, possibly affected by diabetic pathology concomitant with the cardiopathy.

[0016] Preferably, the content of EPA and/or DHA and/or of the at least one derivative thereof is between 50% and 100%, in particular between 75% and 95%, and more preferably about 85% by weight on the total fatty acid weight. The preferred EPA and/or DHA derivatives are selected from the corresponding C_1 - C_3 alkyl esters and/or from their salts with pharmaceutically acceptable bases such as sodium hydroxide, lysine, arginine or aminoalcohols such as choline. The ethylesters of EPA and DHA, in particular mixed together in any concentration and percentage, are the most preferred.

[0017] The drug is administered preferably orally, in particular in the form of soft gelatin capsules. For oral use, the unit dose generally comprises 100-1000 mg of polyunsaturated fatty acids of the ω -3 series, preferably 500-1000 mg or 300-500 mg, the total dose being usually around 0.1-3.0 g per day or per alternate day, according to the case concerned, and preferably 0.3-2.0 g per day and in particular 1.0 g per day. The effective dose of the drug suitable for the use of the invention is 1.0-60.0 mg/kg of body weight/day.

[0018] Other types of formulation for oral administration are also suitable for the purposes of the invention; for example hard capsules or tablets, in which the polyunsaturated fatty acids are adsorbed on solid supports. It is also possible to use emulsions, granulates in dispersing excipients, syrups, droplets, etc., and other forms of administration able to ensure systemic absorption of the drug, such as sterile solutions or emulsions and the like, suitable for parenteral use and the like, as evaluated by the expert of the art, on the basis of the severity of the pathology.

[0019] Those compositions illustrated in the European Pharmacopea 2000 (EuPh. 2000), containing quantities greater than or equal to 80 wt % of mixtures of EPA and DHA ethylesters and a total of ω -3 polyunsaturated fatty acid ethylesters greater than or equal to 90 wt % are also suitable for the purposes of the present invention.

[0020] The aforestated compositions and the drugs suitable for the use of the invention can be prepared by methods known to the expert of the art, such as those described in U.S. Pat. No. 5,130,061, WO 89/11521, IT 1235879, JP 02/25447, which are incorporated into the present description with regard to the method of preparation.

[0021] The drug suitable for use according to the present invention can also comprise other active principles and/or drugs, in association, possessing activity complementary to or synergic with that of the drug suitable for use according to the invention, and also at least one pharmaceutically acceptable vehicle and/or one diluent and/or one surfactant and/or one thickener and/or one binder and/or one lubricant and/or one aromatizer and/or one colorant and/or one stabilizer and the like, which can easily be selected by the expert of the art. Of the stabilizers, antioxidants such as vitamin E (tocopherol), ascorbyl palmitate, ascorbic acid, hydroxytoluene and the like, which can be easily selected by the expert of the art, are particularly preferred.

[0022] According to another aspect, the invention relates to a method for the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, comprising the administration of an effective dose of a drug comprising polyunsaturated fatty acids of the ω -3 series as hereinbefore described. In particular, the method of the invention is indicated whenever the occurrence of a major cardiac event is predicted such as an infarct, in particular of the myocardium, death from a cardiological cause or sudden death.

[0023] The following examples illustrate the invention but without limiting it.

[0024] The compositions illustrated in the following table were prepared by the methods described in U.S. Pat. No. 5,130,061 (compositions A, C, D, F), IT 1235879 (composition B), JP 02/25447 (composition E) and WO 89/11521 (compositions G-I).

[0025] All the quantities indicated in the following table express percentages by weight on the total weight of polyunsaturated fatty acids of the ω -3 series.

	A ¹	B ¹	C ¹	D ¹	E ¹	F ¹	G ¹	H ²	I ³
EPA	>40	>44	>40	>25	>80	>20	<15	>40	>40
DHA	>34	>30	>34	>20	<10	>25	>80	>30	>30
EPA + DHA	>85	>80	>80	>50	>80	>50	>85	>80	>80
esters ⁴		>3	—						
tot.esters ⁵			>90						
α -tocopherol	0.03	0.03	0.1	0.3	0.1	0.3	0.03	0.1	0.1

¹-ethyl esters; ²-acids; ³-sodium salts; ⁴-ethyl esters of other (C_{20} , C_{21} , C_{22}) ω -3 acids; ⁵-total ethyl esters of ω -3 acids.

EXAMPLE 2

[0026] The compositions illustrated in the following table, relative to soft gelatin capsules containing 1 g of polyunsaturated fatty acid ethyl esters, were prepared by methods known in the art.

	A (mg)	B (mg)	C (mg)
EPA ¹	525	—	>400
DHA ¹	315	—	>340
EPA + DHA		850	>800
Total ω-3 ¹		—	>900
d-α-tocopherol	4 I.U.	—	4 I.U.
d,l-α-tocopherol		0.3	
gelatin	246	—	246
gelatin succinate		233	
glycerol	118	67	118
OFR	2.27	—	2.27
OFG	1.27		1.27
SOB		1.09	
SPOB		0.54	

¹-ethyl esters; OFR: red iron oxide OFG: yellow iron oxide; SOB: sodium p-oxybenzoate; SPOB: sodium propyl p-oxybenzoate; I.U.: international units.

[0027] Pharmacological Activity

[0028] The pharmacological activity of the compositions of the invention was evaluated on the basis of tests carried out on small laboratory animals (mouse, guinea pig, rat); this experimental model was chosen because of the ability to make rapid and highly reproducible verifications and to use a sufficiently large number of animals, such as to enable a statistically accurate evaluation of the results to be made without exposing the patient to risk, with evident ethical implications.

[0029] During the course of these tests, groups of animals were pretreated repeatedly with the formulations of Examples 1 and 2 and then, in comparison with untreated groups, were subjected to the action of cardiotoxic or respiration-depressive substances, then visually measuring protection against death, or—by means of elettrocardiographic recording—measuring the delay in the start of initial cardiac arrhythmia or of ventricular tachycardia and above all the delay in or the prevention of animal death due to sudden cardiac and/or respiratory arrest.

[0030] Using an analogous experimental model, cardiolo-gical pathology, coronary ischemia and a state of infarct were induced by coronary ligation instead of by cardiotoxic agents.

[0031] Test 1

[0032] The experimental sudden death model was obtained by cardiac arrest induced by intravenous (i.v.) administration of a cardiotoxic agent (ouabain). In prelimi-nary tests, various doses of ouabain were administered to non-anesthetized guinea pigs of both sexes of weight 300-380 g, in order to determine the minimum lethal dose for 100% of the animals within 15 minutes from i.v. injection (240 mg/kg, intravenously administered over 3 minutes).

[0033] Two groups of 20 guinea pigs were then treated with 50 and 100 mg/kg of a composition containing 85% of EPA and DHA ethylesters (Ex. 1, composition A) for 10 days. After 2 hours from the last administration the two

groups of guinea pigs and a further untreated group, used as control, were treated with 240 mg/kg i.v. of ouabain, record-ing mortality within the subsequent 15 minutes.

[0034] Results expressed as survivors after 15 minutes:

Controls	00/20
50 mg/kg	11/20
100 mg/kg	16/20

[0035] Test 2

[0036] 3 groups of 15 male mice, initial weight 25-32 g, were treated orally for 15 days with physiological solution (control group) and with 50 or 100 mg/kg of a composition containing 85% of EPA and DHA ethylesters (Ex. 1, com-position A).

[0037] 60 minutes after the end of the last treatment, the animals of all the groups were treated with sodium pent-abarbital i.p. (50 mg/kg) and then with aconitine i.v. (0.25 mg/kg). The times of appearance of cardiac arrhythmia (deviation >5 seconds from the normal sinus rhythm), of ventricular fibrillation and of cardiac arrest were determined by electrocardiograph recording. Results expressed as mean±standard deviation (seconds) on the positive animals.

T	t ₁ (sec)	t ₂ (sec)	t ₃ (sec)	S
C	123 ± 12 (15/15)	174 ± 7 (15/15)	214 ± 32 (15/15)	00/15
50 mg/kg	168 ± 8 (08/15)	235 ± 16 (06/15)	350 ± 26 (06/15)	09/15
100 mg/kg	195 ± 15 (05/15)	284 ± 18 (03/15)	378 ± 35 (03/15)	12/15

T-treatment; t₁-time of appearance of arrhythmia (number of animals); t₂-time of appearance of fibrillation (number of animals); t₃-time of car-diac arrest (number of animals); S-survivors after 15 minutes; C-control (with physiological solution).

[0038] Test 3

[0039] 2 groups of 20 male rats, initial weight 310-350 g, were treated orally for 15 days with physiological solution (control group) and with 100 mg/kg of a composition containing >80% of EPA and DHA ethylesters (Ex. 1, composition B). The rats of the 2 groups were then anes-thetized with sodium pentobarbital i.p. (50 mg/kg), then subjected to ligation of the left anterior descending coronary artery, which allows blood flow to the left ventricle, so inducing an acute ischemic state of the myocardium. During the subsequent 15 minutes the duration of ventricular fibril-lation was recorded by ECG, this either resolving itself spontaneously or concluding with sudden death.

[0040] Results

T	F (sec)	Mortality	S (%)
C	190 ± 24 (18/20)	16/20	20
100 mg/kg	55 ± 5 (04/20)	01/20	95

T-treatment; F-duration of fibrillation; S-survivals after 15 minutes; C-con-trol (with physiological solution).

[0041] Test 4

[0042] The experimental model implemented for sudden death by respiratory arrest involves its inducement by chloroform inhalation.

[0043] 4 groups of 10 male mice, initial weight 26-32 g, were treated orally for 5 days with physiological solution (control group) and with 10, 30 and 60 mg/kg of a composition containing 80% of EPA and DHA ethylesters (Ex. 1, composition C).

[0044] 60 minutes after the end of the last treatment, the animals were exposed to chloroform until respiratory arrest had occurred. The animals were then checked for tachyarrhythmia of the myocardium induced by the hypoxic state, this either resolving itself spontaneously within the next 15 minutes or concluding with death of the animal.

[0045] Results

Treatment	Protection from tachyarrhythmia	Survivals
Control	00/10	03/10
10 mg/kg	04/10	06/10
30 mg/kg	07/10	08/10
60 mg/kg	09/10	10/10

[0046] Test 5

[0047] 2 groups of 20 male rats were treated as on Test 3, with physiological solution and with the same EPA and DHA composition (Example 1, composition B).

[0048] Ligature of the circumflex coronary artery was then effected, with consequent reduction in the contractile capacity of the myocardium and of the ejection fraction. The mortality of 18/20 animals of the control group fell to 4/20 of the treated group, during the course of the subsequent 60 minutes.

[0049] The clinical results of the tests demonstrate the pharmacological activity of the polyunsaturated fatty acids of the ω -3 series in the primary prevention of major cardiovascular events in subjects who have not undergone previous infarct episodes.

1. Use of polyunsaturated fatty acids of the ω -3 series for the preparation of a drug useful in the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, wherein the fatty acids comprise eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) and/or at least one pharmaceutically acceptable derivative thereof, in quantities greater than or equal to 25 wt % on the total fatty acid weight.
2. Use as claimed in claim 1, wherein the major cardiovascular event is infarct.
3. Use as claimed in claim 1, wherein the major cardiovascular event is infarct of the myocardium.
4. Use as claimed in claim 1, wherein the major cardiovascular event is death from a cardiological cause.
5. Use as claimed in claim 1, wherein the major cardiovascular event is sudden death.
6. Use as claimed in any one of the preceding claims, wherein the subjects are cardiopathic.

7. Use as claimed in any one of the preceding claims, wherein the subjects are affected by coronary ischemia.
8. Use as claimed in any one of the preceding claims, wherein the subjects are affected by arrhythmia, fibrillation, electrical hyperexcitability of the myocardium cells, disorder of diffusion of the electrical excitement and of electrical conduction of the myocardium.
9. Use as claimed in any one of the preceding claims, wherein the subjects are affected by cardiac disorders of mechanical type.
10. Use as claimed in any one of the preceding claims, wherein the subjects are affected by cardiac insufficiency.
11. Use as claimed in any one of the preceding claims, wherein the subjects are affected by cardiac decompensation.
12. Use as claimed in any one of claims from 6 to 11, wherein the subjects are affected by diabetic pathology concomitant with cardiopathy.
13. Use as claimed in any one of the preceding claims, wherein the content of EPA and/or DHA and/or of the at least one derivative thereof is between 50% and 100% by weight on the total fatty acid weight.
14. Use as claimed in any one of the preceding claims, wherein the content of EPA and/or DHA and/or of the at least one derivative thereof is between 75% and 95% by weight on the total fatty acid weight.
15. Use as claimed in any one of the preceding claims, wherein the content of EPA and/or DHA and/or of the at least one derivative thereof is equal to about 85% by weight on the total fatty acid weight.
16. Use as claimed in any one of the preceding claims, wherein the at least one derivative of EPA and/or DHA is selected from the corresponding C₁-C₃ alkyl esters and/or acids and/or salts with pharmaceutically acceptable bases.
17. Use as claimed in any one of the preceding claims, wherein the drug comprises EPA ethylester and/or DHA ethylester.
18. Use as claimed in any one of the preceding claims, wherein the drug is administered orally.
19. Use as claimed in any one of the preceding claims, wherein the drug is in the form of soft gelatin capsules.
20. Use as claimed in any one of the preceding claims, wherein the drug is administered at a dose of 0.1-3.0 g per day.
21. Use as claimed in any one of the preceding claims, wherein the drug is administered at a dose of 0.3-2.0 g per day.
22. Use as claimed in any one of the preceding claims, wherein the drug is administered at a dose of 1.0 g per day.
23. A method for the primary prevention of a major cardiovascular event in subjects who have not undergone previous infarct episodes, comprising the administration of an effective dose of a drug claimed in any one of the preceding claims.
24. A method as claimed in the preceding claim, wherein the major cardiovascular event is infarct.
25. A method as claimed in claim 23, wherein the major cardiovascular event is infarct of the myocardium.
26. A method as claimed in claim 23, wherein the major cardiovascular event is death from a cardiological cause.
27. A method as claimed in claim 23, wherein the major cardiovascular event is sudden death.

* * * * *



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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.

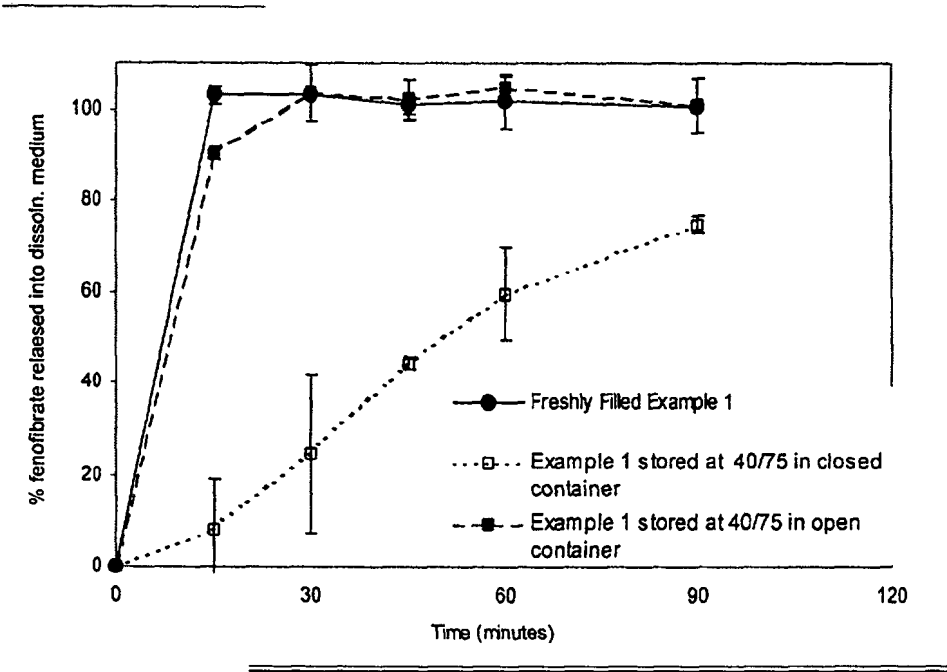


FIG. 1

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, nutraceutical, 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

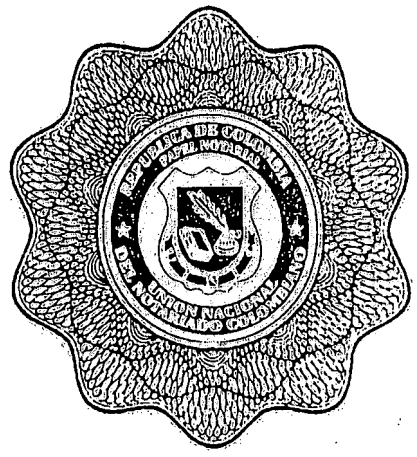
less than about 10% w/w in the fill material. In another aspect, the solubility of the plasticizing agent in the fill material may be less than about 5% w/w. In yet another aspect, the solubility may be less than about 1% w/w. In a further aspect, the solubility of the plasticizing agent may be less 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

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ESCRITURA NUMERO CUATRO MIL QUINIENTOS -
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del mes de OCTUBRE del año DOS MIL UNO --

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

compareció JUAN MANUEL BARBERI OSPINA mayor de edad, vecino de Cali,
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SEGUNDO: Que en tal carácter, por este público instrumento, concede Poder Especial
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con dirección carrera 7 No. 88.23 oficina 205, de la misma ciudad, como su representante
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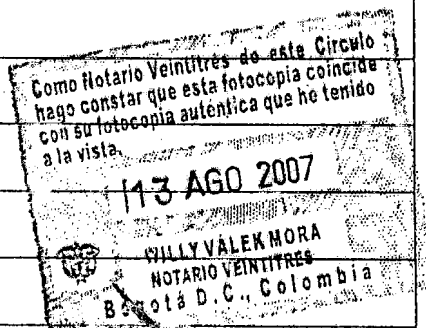
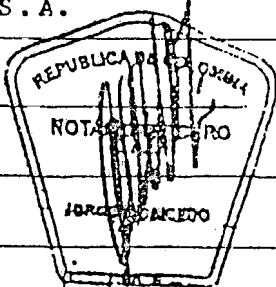
Leído el presente instrumento al otorgante, lo aprobó y en constancia firma conmigo el Notario de todo lo cual doy fe.-----

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

91 *Juan m Barberi*

JUAN MANUEL BARBERI OSPINA

En rep. de TECNOQUIMICAS S.A.



El Notario Tercero de Cali

Dr. JORGE ENRIQUE CAICEDO ZAMORANO

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				Bogotá D.C., Septiembre 27 de 2012 - 16:02:15	
RECIBIDO DE : REYES Y REYES ABOGADOS				NI 900.048.328	
*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	200604250	27/09/2012	2.075.000.00
*** Conceptos Pagados ***					
CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO	
1 50005-01-04	PRESENTACION DE OBSERVACIONES A SOLICITUDES	12 MARCAS Y LEMAS COMERCIALES	315.000.00	315.000.00	
				\$315.000.00	
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SON: **TRESCIENTOSQUINCE MIL PESOS MONEDA CORRIENTE**					
Responsable: _____					
Recibo de Caja Aplicado al Expediente No. _____					
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO					
					
No. 11-163902- -00005-0000					
Fecha: 2012-09-27 17:03:36 Dep. 2020 DIR.NUEVASCR					
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI					
Act. 400 OPOSIOBSERVTER Folios: 29					
Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia					
Web: www.sic.gov.co e-mail: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240					
Septiembre 27 de 2012 - 16:02:16					

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

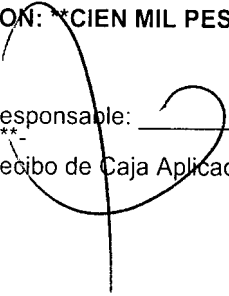
 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 12 - 0099311
		Bogotá D.C., Septiembre 27 de 2012 - 16:02:15

RECIBIDO DE : REYES Y REYES ABOGADOS	NI 900.048.328
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*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	200604250	27/09/2012	2.075.000.00

*** Conceptos Pagados ***			
CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO Vr.CONCEPTO
1 50005-01-08	PRORROGA DE TERMINOS	1609 S.DISTINTIVOS PRORROGA DE TERMINOS O PLAZO ADICIONAL	100.000.00 100.000.00
			\$100.000.00
=====			

SON: *CIEN MIL PESOS MONEDA CORRIENTE***

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-163902- -00005-0000
Fecha: 2012-09-27 17:03:36 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 29