



(51) International Patent Classification:

A61K 8/11 (2006.01) A61K 8/34 (2006.01)
A61K 8/49 (2006.01) A61Q 19/00 (2006.01)
A61K 8/67 (2006.01)

(21) International Application Number:

PCT/US2016/014980

(22) International Filing Date:

26 January 2016 (26.01.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(71) Applicant: KIMBERLY-CLARK WORLDWIDE, INC.
[US/US]; 2300 Winchester Road, Neenah, Wisconsin
54956 (US).

(72) Inventor: CHEN, Jin; 1326 W. Starview Drive, Appleton,
Wisconsin 54913 (US).

(74) Agents: PIERRE, Kenya T. et al.; KIMBERLY-CLARK
WORLDWIDE, INC., 2300 Winchester Road, Neenah,
Wisconsin 54956 (US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG,
MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM,
PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ,
TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU,
TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE,
DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,
LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,
SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a
patent (Rule 4.17(ii))

Published:

— with international search report (Art. 21(3))

(54) Title: RUPTURE RELEASE MICROCAPSULE FOR SKIN CARE APPLICATIONS

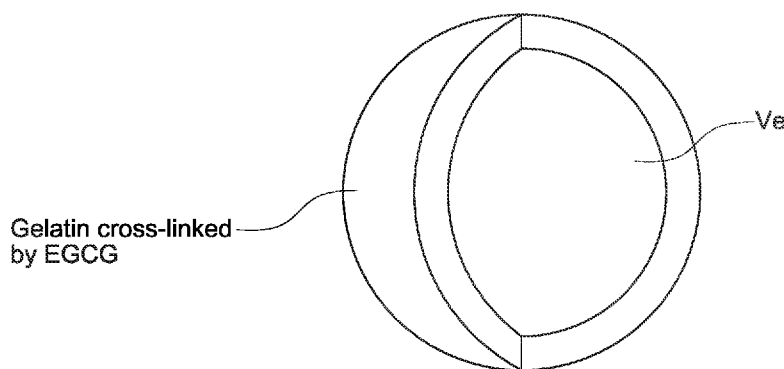


FIG. 1

(57) Abstract: The present invention relates to a crosslinked biocompatible material comprising gelatin and a polyphenol wherein said crosslinked biocompatible material encapsulates and controllably releases from about 5% to about 50% of a hydrophobic, oil-soluble active selected from tocopherol, catechins, lycopene, resveratrol, genistein, proanthocyanidin, and Niacinamide.



RUPTURE RELEASE MICROCAPSULE FOR SKIN CARE APPLICATIONS

FIELD OF THE INVENTION

5 The present invention relates to a gelatin microcapsule structure cross-linked by a dual-functioning flavonoid based polyphenol to deliver an oil-soluble active agent in a controllable manner for skin benefiting agents.

BACKGROUND OF THE INVENTION

10 Catechins are flavonoid-based polyphenols that are known for their antioxidant and neuroprotection activity such as tumor angiogenesis, prevention of atherosclerosis and the modulation of cholesterol metabolism. Epigallocatechin gallate (EGCG), the major constituent of catechin-based flavonoids in green tea, has been found to have antioxidant, immunomodulatory, photoprotective, anti-angiogenic, and anti-inflammatory properties. Because of the properties of EGCG, topical application may offer sun damage protection by quenching free radicals and reducing inflammation in addition to
15 protection against oxidative cellular damage caused by harmful ultraviolet (UV) rays. Specifically, EGCG has been demonstrated to protect epidermal cells against damage induced by ultraviolet B (UVB) radiation. Thus, the incorporation of this compound in personal and beauty care products, hygiene, health care and other skin-contacting products has become increasingly beneficial.

20 A large number of functionally active chemicals have been known for use with various skin-contacting products. However, many of these functionally-active chemicals are not stable or do not have ideal properties under various environmental conditions. Additionally, many of these actives contain aldehyde-based formulations that are not considered natural or desirable within skin-care products. Additional challenges presented by the use of such active chemicals include the difficulties involved with gradually controlling the release of such active chemicals, as well as the potential side effects and costs
25 resulting from use of chemically degraded products. Other actives, such as antioxidants, are also often not stable when exposed to ambient conditions. Antioxidants can readily be oxidized by oxygen in the air. Some skin-repairing chemicals are also not stable when exposed to the surrounding environment. For example, the skin-repairing agent retinol is not stable under ambient conditions without protection from the environment. In fact, it can become a skin irritant when its concentration is relatively high.

30 Attempts have been made to overcome the stability and storage limitations presented by such actives. For example, some have suggested stabilizing retinol by encapsulating it in pH-sensitive

polymers and then releasing it at a later time by changing the solubility of the encapsulating matrix through a pH change. The encapsulated retinol still suffers significant degradation, presumably from oxidation. Others have suggested converting retinol into an ester as a proactive (a precursor to the retinol active), and then at a later time converting the ester into the active form by use of enzymes present in a user's body after delivery through a user's skin. With such methodology, however, only a small portion of the ester is used effectively by the skin layer and a majority of the esters are wasted by the system. Such a system can also actually lead to side effects when too much retinol ester is used to achieve effective dosages on the skin. Existing encapsulation chemistries for consumer products often leak or release prematurely. Therefore, a need still exists for delivery compositions for skin-repair actives. It would even be more beneficial for the delivery system to not only deliver the active, but also contribute to the benefits and active ingredients. Currently, no proactive technology has emerged to be very effective to work both as a skin benefit agent and at the same time controllably release or release-on-demand under mild conditions. A need, therefore, exists for a versatile composition that effectively delivers beneficial skin care actives, and releases such actives controllably.

SUMMARY OF THE INVENTION

The present invention relates to a crosslinked biocompatible material comprising gelatin and a polyphenol wherein said crosslinked biocompatible material encapsulates and controllably releases from about 5% to about 50% of a hydrophobic, oil-soluble active selected from tocopherol, catechins, lycopene, resveratrol, genistein, proanthocyanidin, and Niacinamide.

BRIEF DESCRIPTION OF THE DRAWINGS

A full and enabling disclosure of the present invention is set forth more particularly in the remainder of the specification, including reference to the accompanying figures, in which:

FIG. 1 illustrates the core-shell structure of the present invention wherein EGCG is cross-linked with gelatin to microencapsulate Vitamin E.

FIG. 2A shows an intact optical micrograph image of an EGCG cross-linked gelatin vitamin E microcapsule.

FIG. 2B shows a ruptured optical micrograph image of an EGCG cross-linked gelatin vitamin E microcapsule.

DETAILED DESCRIPTION OF THE INVENTION

While the specification concludes with the claims particularly pointing out and distinctly claiming the invention, it is believed that the present invention will be better understood from the following description.

All percentages, parts and ratios are based upon the total weight of the compositions of the present invention, unless otherwise specified. All such weights as they pertain to listed ingredients are based on the active level and, therefore; do not include solvents or by-products that may be included in commercially available materials, unless otherwise specified. The term "weight percent" may be denoted as "wt. %" herein. Except where specific examples of actual measured values are presented, numerical values referred to herein should be considered to be qualified by the word "about".

The use of any trademarks herein has been noted with CAPITALIZATION of the word wherever it appears to acknowledge and respect the proprietary nature held by the owners of the mark. The word is followed by the generic terminology only wherever it appears for the first time herein.

The present disclosure pertains to a composition comprising EGCG that not only aids in the controlled release of functionally active components, it also serves to provide the anti-oxidant properties desired by the formulation. The EGCG serves to gradually or rapidly release active skin care agents upon the occurrence of specific environmental stimuli. The composition can be used in bandages, hygiene products, health care products and skin-contacting beauty products, as well as in other consumer product applications.

Polyphenols

The present invention utilizes a flavonoid-based polyphenol to crosslink with a protein such as gelatin in order to form a core-shell structured microcapsule that will allow for the controlled release of an active. It is preferred that the flavonoid-based polyphenol is a catechin and more particularly, epigallocatechin gallate (EGCG). However, the polyphenol may be selected from the group consisting of EGCG, tannic acid, epicatechin and mixtures thereof. Through coacervation, the microcapsules provide a unique release mechanism to deliver active ingredients and protect the encapsulated actives. EGCG provides antioxidant properties that are important and beneficial to skin health. Thus, not only does EGCG provide beneficial actives, it also has the capacity to act as a gelatin crosslinking agent and further improve the oxygen barrier properties of gelatin through free radical quenching property, which is an advantage over glutaraldehyde.

The present invention provides that the ratio of EGCG to gelatin by weight is 1:5. The amount of active, for example, vitamin E that is encapsulated may be from about 5%, from about 15% or from about 25% to about 40% to about 45% or to about 50%, by weight of the capsule.

Coacervation

- 5 First developed by the National Cash Register Company (NCR), complex coacervation has been employed as an important method for the microencapsulation of various solid and liquid ingredients. In the complex coacervation process gelatin having a high iso-electric point and gum arabic containing many carboxyl groups are added to a core-containing suspension at a relatively low pH above 35° C. The gelatin and gum arabic react to form microdroplets of polymer coacervate which separate.
- 10 At pH values above 6 both the gelatin and gum arabic materials are miscible, however when the pH is lowered below gelatin's isoelectric point, the net charge on the gelatin becomes negative and it then interacts with the positively charged gum arabic. As the pH is lowered to about 4.5, microcapsules form from coacervate material positively charged gelatin and negatively charged gum arabic depositing around the oil droplets. After wall formation, the wall around the core is hardened typically by the
- 15 crosslinking of an inorganic salt such as polyphosphate or an aldehyde such as formaldehyde, glutaraldehyde, Urea Formaldehyde (UF), Melamine Formaldehyde (MF), and the like. Because of the crosslink structure, the microcapsules have good thermal and moisture-resistant properties that can be used for controlled release applications. In the final steps, the suspension of microcapsules is cooled and the pH raised. The suspension is then filtered leaving the microcapsules on the filter media.
- 20 Although effective, microencapsulation utilizing only the foregoing components can create a problem wherein the production of the microcapsules yields only a certain percent that successfully encapsulates a liquid core without leaking. Additionally, gelatin is prone to degradation with concomitant odor of ammonia possibly being exuded. Although many alternative materials (e.g. alginates, chitosan, starch, poly (L-lysine), whey protein and methyl cellulose) can be used, the most commonly used are
- 25 mixtures of proteins and anionic polysaccharides. Commonly, gelatin and gum arabic are used for microencapsulation. And, preferably, gelatin is used. To combat issues such as degradation, however, a crosslink agent is used to provide a more stable and functional microencapsulation.

EGCG as a Crosslink Agent

- In addition to functioning as a skin-care benefit, the EGCG provides the benefits to the present
- 30 invention by also functioning as the cross-linking agent used to encapsulate additional active agents as disclosed herein and shown in FIG. 1. As stated, inorganic salts and aldehydes are commonly used as cross-linking agents for microencapsulation of liquids and solids. The present invention avoids the use

of aldehydes, however, because they are not plant-derived and thus are not considered natural elements that arrive at the objective of the present invention in creating a commercially, "natural" skin care formula. Additionally, although glutaraldehyde is widely used as a crosslink material, many adverse health effects on humans such as chronic bronchitis and nasal symptoms have been reported in association with glutaraldehyde exposure (J. Occup. Health. 48(2), 75-87, 2006).

The crosslink component of the present invention should comprise at least one ionic component such as a polyphenol. Preferably, the present invention provides a polyphenol such as EGCG to crosslink with the biocompatible gelatin. Gelatin is a derivative of collagen and one of the most common extracellular matrix (ECM) proteins. Natural gelatin has the drawback of dissolving in an aqueous environment and, therefore, requires a crosslinking procedure using appropriate agents. The typical structure of gelatin is:



The strong interaction between EGCG and gelatin within the present invention is a combination of hydrogen bonding and pi stacking (phenol ring with proline residue on gelatin). EGCG cross-linked gelatin and a skin beneficial ingredient, such as an oil soluble tocopherol, forms a core-shell spherical structure through complex coacervation process. Through a controlled release mechanism such as a mechanical rupturing, such as a finger press, the ingredient trapped in the core is able to be available to offer a unique benefit to consumers. In addition, the EGCG-gelatin complex microencapsulated core offers the delivery of additional antioxidant benefits.

The present invention is able to successfully synthesize the core-shell structure with a size of from about 50 μm to about 100 μm . When crushed via finger or by mechanical means such as a CARVER® hydraulic bench top press, approximately 90% of the actives are able to be released.

Active Ingredients

Although the EGCG can also be considered an active ingredient, the crosslinked EGCG-Gelatin material encapsulates hydrophobic, oil-soluble active ingredients within the EGCG-Gelatin core structure to offer the synergistic skin health benefits sought by consumers. Thus, active ingredients of the present invention that may be included within the encapsulation include, but are not limited to, tocopherol (Vitamin E), catechins, lycopene, resveratrol, genistein, proanthocyanidins (such as grape seed extract), and Niacinamide (Vitamin B₃). They can be found in the present invention in an amount of from about 5%, from about 15% or from about 25% to about 40% to about 45% or to about 50%, by weight of the capsule. The amount of active ingredient within the capsule can be determined by any analytical method such as high-performance liquid chromatography (HPLC) analysis (using a detector such as WATERS®

2487 with dual λ absorbance detector). HPLC is the technique used to separate and quantify each component in a mixture. The components of the sample are separated from one another by the column packing that involves various chemical and/or physical interactions between their molecules and the packing particles. The separated components are collected and identified by spectrophotometer as detailed in Example 1.

The present invention is useful to incorporate into a variety of consumer personal care products such as a cream, lotion, body/hair shampoo, cleanser, wipe, absorbent articles, and health & hygiene products such as bandages and skin creams, ointments, lotions, oils and the like.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention, as many variations thereof are possible without departing from the spirit and scope of the invention.

EXAMPLE 1

Gelatin was used as the shell material and cross-linked with EGCG. To facilitate encapsulation, the vitamin E was diluted 60:40 with soybean oil. Vitamin E encapsulated gelatin via complex coacervation was treated with EGCG at 20% by weight relative to the gelatin. 4.5 g of 300Å gelatin was dissolved in to 450 mL of deionized water under argon gas with overhead stirring at 325 rpm in a 55°C bath. 11.7 g of vitamin E was dissolved in 7.2 g soybean oil, added to the gelatin solution and homogenized for 1.5 min at 5k rpm. 0.45 g polyphosphate was dissolved in to 10 mL deionized water and then added to the aqueous gelatin solution. 10% acetic acid solution was then used to adjust the pH to 5.01. The heat was removed and the emulsion cooled under ambient room conditions to room temperature. 0.9 g EGCG was dissolved in 10 mL water and then added to crosslink the capsules overnight under gentle stirring. After crosslinking the capsule were washed twice using centrifugation and deionized water for rinsing. The capsules were then frozen with liquid nitrogen and lyophilized for 48 hrs resulting in a dry power.

The capsules were loaded with approximately 42.6% of Vitamin E, as determined by High-performance liquid chromatography (HPLC) analysis (WATERS® 2487 with dual λ absorbance detector). The mobile phase was a 95:5 mixture of methanol and purified water with a Supelco Discovery C-18 column. 10 mg of capsules were dissolved into 1 mL of Dimethyl sulfoxide (DMSO) and 30 mL of ethanol, followed by sonication and vortexing. A 1 mL aliquot was filtered through a 0.45 μ m syringe filter and diluted 1:1 with ethanol prior to injection into the HPLC. As shown in FIG. 2A, the resulting capsules

have a core-shell morphology with a size 50 μm - 100 μm as determined by an optical micrograph image.

Core-shell capsules can release actives through diffusion or mechanical release. Mechanical release was studied for this application. To mimic skin application, 20 mg of capsules were placed
5 between two glass slides and gently pressed while rubbing for 30 seconds. Optical micrograph images (FIGS. 2A and 2B) show significant change before and after as an indication of liquid core being squeezed out of rupture capsules. Alternatively, the capsules were placed in a CARVER® hydraulic bench top press at 1000 psi. Both intact and crushed capsules were added directly to octanol, resulting in 73% and 91% Vitamin E, respectively, recovered after 5 min of soaking. This indicates that Vitamin E
10 is present and then released after crushing.

The dimensions and values disclosed herein are not to be understood as being strictly limited to the exact numerical values recited. Instead, unless otherwise specified, each such dimension is intended to mean both the recited value and a functionally equivalent range surrounding that value. For example, a dimension disclosed as "40 mm" is intended to mean "about 40 mm".

15 All documents cited in the Detailed Description of the Invention are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention. To the extent that any meaning or definition of a term in this written document conflicts with any meaning or definition of the term in a document incorporated by reference, the meaning or definition assigned to the term in this written document shall govern.

20 While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

CLAIMS

What is claimed is:

1. A crosslinked biocompatible material comprising gelatin and a polyphenol wherein said crosslinked biocompatible material encapsulates and controllably releases from about 5% to about 50% of a hydrophobic, oil-soluble active selected from tocopherol, catechins, lycopene, resveratrol, genistein, proanthocyanidin, and Niacinamide.
2. The crosslinked biocompatible material of claim 1 wherein the polyphenol is epigallocatechin gallate.
3. The crosslinked biocompatible material of claim 2 wherein the ratio of epigallocatechin gallate to gelatin by weight is 1:5.
4. The crosslinked biocompatible material of claim 1 wherein the core-shell morphology is from about 50 μm to about 100 μm .
5. The crosslinked biocompatible material of claim 1 wherein 20% or more of the actives are able to be released after the encapsulation is crushed.
6. The crosslinked biocompatible material of claim 1 wherein the encapsulation is formed by coacervation.
7. The crosslinked biocompatible material of claim 1 wherein said material is included in a personal care product.

1/1

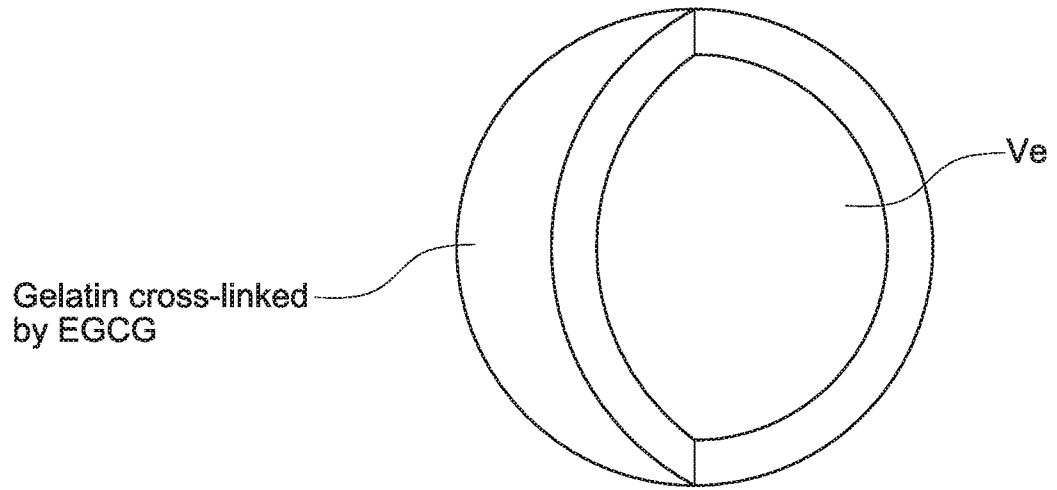


FIG. 1

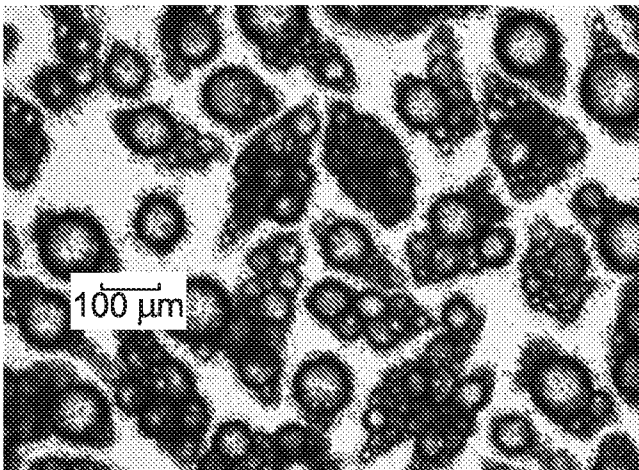


FIG. 2A

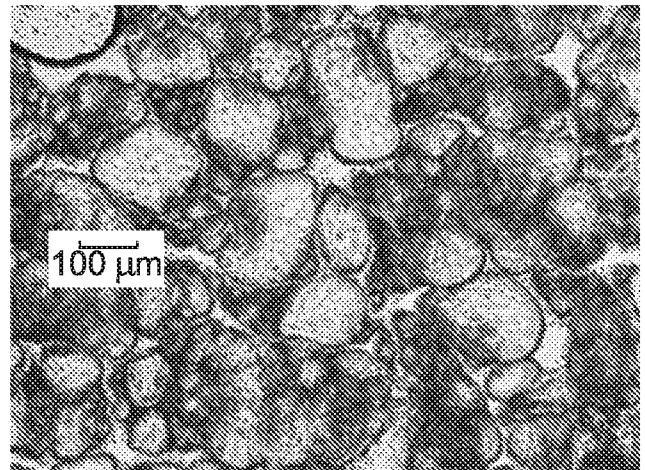


FIG. 2B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/014980**A. CLASSIFICATION OF SUBJECT MATTER****A61K 8/11(2006.01)i, A61K 8/49(2006.01)i, A61K 8/67(2006.01)i, A61K 8/34(2006.01)i, A61Q 19/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 8/11; A61K 9/14; B01J 13/02; A23L 1/00; A61L 27/44; A61L 27/50; A61K 9/50; A61K 35/78; A23P 1/04; A61K 47/00; A61K 8/49; A61K 8/67; A61K 8/34; A61Q 19/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: microcapsule, gelatin, polyphenol, encapsulation, coacervation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6969530 B1 (CURTIS, JONATHAN MICHAEL et al.) 29 November 2005 See claims 1, 12, 20, 23, 31, 50-51, 68 and 70; figure 2; column 3, lines 18-21; column 9, lines 41-46.	1,4-7
A		2-3
A	EP 1492417 B1 (OCEAN NUTRITION CANADA LTD.) 15 November 2006 See claims 1-3, 5-6, 46, 88 and 91.	1-7
A	WO 2014-126537 A1 (AGENCY FOR SCIENCE, TECHNOLOGY AND RESEARCH) 21 August 2014 See claims 1 and 16-18.	1-7
A	US 5780060 A (LEVY, MARIE-CHRISTINE et al.) 14 July 1998 See claims 1-2 and 8.	1-7
A	US 2009-0104251 A1 (LEE, PHILLIP K.) 23 April 2009 See claims 1-5.	1-7



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

21 October 2016 (21.10.2016)

Date of mailing of the international search report

21 October 2016 (21.10.2016)

Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

189 Cheongsa-ro, Seo-gu, Daejeon, 35208, Republic of Korea

Facsimile No. +82-42-481-8578

Authorized officer

CHO, KI YUN

Telephone No. +82-42-481-5655



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/014980

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6969530 B1	29/11/2005	AU 2006-213503 A1	17/08/2006
		AU 2006-213503 B2	06/01/2011
		CA 2541931 A1	21/07/2006
		CA 2541931 C	21/08/2007
		EP 1846153 A2	24/10/2007
		EP 1846153 B1	06/11/2013
		US 2006-0165990 A1	27/07/2006
		US 8034450 B2	11/10/2011
		WO 2006-085227 A2	17/08/2006
		WO 2006-085227 A3	08/02/2007
EP 1492417 B1	15/11/2006	AT 345053 T	15/12/2006
		AT 457652 T	15/03/2010
		AU 2003-218573 A1	27/10/2003
		AU 2003-218573 B2	08/12/2005
		CA 2455971 A1	23/10/2003
		CA 2455971 C	27/06/2006
		CN 100522338 C	05/08/2009
		CN 101574327 B	03/08/2011
		CN 1646029 C	27/07/2005
		DE 60309684 T2	11/10/2007
		DK 1492417 T3	26/02/2007
		DK 1736060 T3	07/06/2010
		EP 1492417 A1	05/01/2005
		EP 1736060 A2	27/12/2006
		EP 1736060 A3	09/05/2007
		EP 1736060 B1	17/02/2010
		EP 1736060 B2	08/06/2016
		ES 2277072 T3	01/07/2007
		ES 2340703 T3	08/06/2010
		HK 1076993 A1	26/03/2010
		JP 2005-522313 A	28/07/2005
		JP 2011-025242 A	10/02/2011
		JP 2013-177400 A	09/09/2013
		JP 5372310 B2	18/12/2013
		JP 5597486 B2	01/10/2014
		JP 5896954 B2	30/03/2016
		KR 10-0811284 B1	07/03/2008
		KR 10-2004-0105865 A	16/12/2004
		MX 252867 B	19/12/2007
		MX 308546 B	08/04/2013
		NZ 535687 A	31/03/2006
		PT 1492417 E	28/02/2007
		US 2003-0193102 A1	16/10/2003
		US 2005-0019416 A1	27/01/2005
		US 2010-0209524 A1	19/08/2010
		US 6974592 B2	13/12/2005
		US 7727629 B2	01/06/2010
		US 8968872 B2	03/03/2015

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/014980

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		WO 03-086104 A1	23/10/2003
WO 2014-126537 A1	21/08/2014	CN 105120909 A	02/12/2015
		EP 2956185 A1	23/12/2015
		JP 2016-507585 A	10/03/2016
		US 2015-0374838 A1	31/12/2015
US 5780060 A	14/07/1998	CA 2159353 A1	10/08/1995
		CA 2159353 C	10/05/2005
		EP 0691886 A1	15/07/1998
		EP 0691886 B1	28/04/1999
		FR 2715582 A1	04/08/1995
		JP 3583133 B2	27/10/2004
		KR 10-0382044 B1	23/07/2003
		WO 95-21018 A1	10/08/1995
US 2009-0104251 A1	23/04/2009	None	