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Fortsættes ...

DESCRIPTION

BACKGROUND

[0001] Mixed omega-3 fatty acid esters are typically encapsulated in type 2a gelatin capsules containing gelatin (~43.4%), glycerol (~20%) and water (~36.6%) and do not experience stability problems throughout their shelf life. While chemically modified gelatins such as succinated/succinylated gelatin have been used to encapsulate reactive fill ingredients, such gelatin is not approved for use in the U.S. and other markets. F.S.Hom et. al (1975) discloses that the addition of sorbitol should be considered in the design and formulation of capsule shells for oxygen-liable drugs. G. Reich (2004) describes the use of hygroscopic plasticizers or non-hygroscopic plasticizers in the preparation of capsules shells. US 2006/0134178 discloses compositions comprising 99% of EPA ethyl ester and α-tocopherol as an antioxidant with improved oxidative stability. It also proposes the addition of a sesame component with ascorbic acid or ascorbyl fatty acid ester. US 6 193 999 describes the use of non-hygroscopic plasticizer such as maltitol in the preparation of soft gelatin capsules

SUMMARY

[0002] There is provided, according to the invention, a pharmaceutical composition comprising at least 95% eicosapentaenoic acid (EPA) enclosed in a capsule shell, wherein a) the pharmaceutical composition has a baseline peroxide value not greater than 5 Meq/kg and upon storage of the pharmaceutical composition at 25 °C and 60% RH for a period of 6 months, the pharmaceutical composition has a second peroxide value not greater than 8 Meq/kg, b) the capsule shell comprises (i) a film-forming material comprising gelatin but substantially no succinated gelatin, (ii) a hygroscopic plasticizer comprising glycerol, and (iii) a non-hygroscopic plasticizer selected from maltitol, lactitol, xylitol, hydrogenated starch hydrolysate and glucose syrup, wherein the hygroscopic plasticizer and non-hygroscopic plasticizer are present in a weight ratio of about 2:1 to about 6:1. According to the invention, there is also provided such a pharmaceutical composition for use in treating or preventing a cardiovascular-related disease in a subject in need thereof.

[0003] There is provided, according to the invention a pharmaceutical composition comprising at least about 95% ethyl eicosapentaenoate (ethyl-EPA) enclosed in a capsule shell, wherein: a) the ethyl-EPA has a baseline peroxide value not greater than 5 Meq/kg and upon storage of the pharmaceutical composition at 30 °C and 65% RH for a period of 6 months, the ethyl-EPA has a second peroxide value not greater than 5 Meq/kg wherein the capsule shell contains no chemically modified gelatin; b) the capsule shell comprises (i) a film-forming material comprising gelatin in an amount of 50% to 70% by weight of the non-aqueous components, (ii) hygroscopic plasticizer comprising glycerin in an amount of 5% to 15% by weight of the non-aqueous components and sorbitol in an amount of 15% to 25% by weight of the non-aqueous

components, and (iii) a non-hygroscopic plasticizer comprising maltitol in an amount of 3% to 10% by weight of the non-aqueous components.

[0004] There is provided, according to the invention, a pharmaceutical composition comprising at least about 95% ethyl eicosapentaenoate (ethyl-EPA) encapsulated in a capsule shell comprising non-chemically modified gelatin, wherein the capsule shell comprises a hygroscopic plasticizer comprising glycerol and sorbitol, and a non-hygroscopic plasticizer comprising maltitol, wherein the capsule shell has a weight ratio of gelatin to hygroscopic plasticizer of about 4:1 to about 8:1 and a weight ratio of hygroscopic plasticizer to non-hygroscopic plasticizer of about 3:1 to about 5:1 and the gelatin:glycerol ratio is at least 5.1:1.

[0005] We have unexpectedly found that high purity eicosapentaenoic acid (EPA) is more susceptible to oxidative degradation than mixed omega-3-acid ethyl esters. In various examples, the disclosure provides pharmaceutical compositions comprising a fatty acid or a derivative thereof in a capsule shell that resists, hinders, attenuates, or prevents oxidation of the fatty acid or fatty acid derivative, for example to a greater extent than is provided by a standard type IIa capsule shell. According to the invention, the fatty acid comprises eicosapentaenoic acid (EPA) or a derivative of EPA, for example ethyl eicosapentaenoate (ethyl-EPA or E-EPA). In another embodiment, the fatty acid comprises ultra-pure EPA.

[0006] In one example, the disclosure provides a pharmaceutical composition comprising ultra-pure EPA encapsulated in a capsule shell, where the ultra-pure EPA has a baseline peroxide value not greater than about 5 Meq/kg and upon storage of the composition at 23 °C and 50% RH for a period of time, that ultra-pure EPA has a second peroxide value not greater than about 20 Meq/kg.

[0007] In other examples, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell comprising a film forming material and a hygroscopic plasticizer, wherein the weight ratio of film-forming material to hygroscopic plasticizer is not less than about 2.5:1. Further, the capsule shell can optionally comprise a non-hygroscopic plasticizer. In one example, the capsule contains no chemically modified gelatin, for example succinated or succinylated gelatin.

[0008] In still other examples, the present disclosure provides methods of treating or preventing a cardiovascular-related disease using compositions as described herein.

[0009] Embodiments of the present invention, or examples of the present disclosure, will be disclosed in further detail herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010]

Fig. 1 shows dissolution profile of an inventive capsule composition containing ~500 mg E-EPA versus a composition comprising EPA in a succinated gelatin capsule.

Fig. 2 shows bioavailability of 300 mg of EPA in succinated gelatin capsules.

Fig. 3 shows bioavailability of an inventive AMR101 capsule composition containing -500 mg E-EPA.

DETAILED DESCRIPTION

[0011] While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0012] The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." In this manner, slight variations from a stated value can be used to achieve substantially the same results as the stated value.

Polyunsaturated Fatty Acids

[0013] In one example, compositions of the disclosure comprise a polyunsaturated fatty acid as an active ingredient. In another example, compositions of the disclosure comprise EPA as an active ingredient. The term "EPA" as used herein refers to eicosapentaenoic acid (*e.g.* eicosa-5,8,11,14,17-pentaenoic acid) and/or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing.

[0014] In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA is in the form of an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1 - C_5 alkyl ester of EPA. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In still another embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

[0015] In still other embodiments, the EPA comprises ethyl-EPA, lithium EPA, mono, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may

also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

[0016] The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

[0017] In one embodiment, EPA present in a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 96% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA can comprise even higher purity EPA, for example at least 97% by weight EPA or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein. Ultra-pure EPA can further be defined (e.g. impurity profile) by any of the description of EPA provided herein.

[0018] In other embodiments, EPA is present in a composition of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, or about 2500 mg.

[0019] In various embodiments, one or more antioxidants can be present in the EPA (e.g. E-EPA or ultra pure E-EPA). Non-limiting examples of suitable antioxidants include tocopherol, lecithin, citric acid and/or ascorbic acid. One or more antioxidants, if desired, are typically present in the EPA in an amount of about 0.01% to about 0.1%, by weight, or about 0.025% to about 0.05%, by weight.

[0020] In one example, a composition of the disclosure contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about

6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight of total fatty acids, docosahexaenoic acid or derivative thereof such as E-DHA, if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid or derivative thereof such as E-DHA. In still another embodiment, a composition of the invention contains no docosahexaenoic acid or E-DHA.

[0021] In another example, EPA represents at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99%, or 100%, by weight, of all fatty acids present in a composition of the disclosure.

[0022] In another example, a composition of the disclosure contains less than 30%, less than 20%, less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA, or derivative thereof. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA) or derivative thereof such as ethyl-linolenic acid, arachidonic acid (AA) or derivative thereof such as ethyl-AA, docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA, alpha-linolenic acid (ALA) or derivative thereof such as ethyl-ALA, stearadonic acid (STA) or derivative thereof such as ethyl-SA, eicosatrienoic acid (ETA) or derivative thereof such as ethyl-ETA and/or docosapentaenoic acid (DPA) or derivative thereof such as ethyl-DPA.

[0023] In another embodiment, a composition of the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least 96%, at least 97%, or at least 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than 4%, not more than 3%, or not more than 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than 0.6%, 0.5%, or 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20 °C) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20 °C) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (f) the composition contains not more than 20 ppm, 15 ppm or 10 ppm heavy metals, (g) the composition contains not more than 5 ppm, 4 ppm, 3 ppm, or 2 ppm arsenic, and/or (h) the composition has a peroxide value not more than 5, 4, 3, or 2 Meq/kg.

[0024] In another embodiment, a composition useful in accordance with the invention comprises, consists essentially of or consists of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In still another

embodiment, the capsule shell contains no chemically modified gelatin.

[0025] In another embodiment, compositions useful in accordance with the invention comprise, consist essentially of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% by weight ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative thereof such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell. In another embodiment, the capsule shell contains no chemically modified gelatin.

[0026] In another embodiment, compositions useful in accordance with the invention comprise, consist essentially of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl eicosatetraenoate and about 0.075% to about 0.25% by weight ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel- or liquid-containing capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

[0027] In another embodiment, compositions useful in accordance with the invention comprise, consist essentially of or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% by weight ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (*e.g.* tocopherol) in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the

composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In another embodiment, the capsule shell contains no chemically modified gelatin.

[0028] In various examples, the disclosure provides a polyunsaturated fatty acid such as EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a pharmaceutical capsule shell. In one example, the capsule shell resists, hinders, attenuates, or prevents oxidation of the fatty acid or fatty acid derivative. In another example, the capsule shell resists, hinders, attenuates, or prevents oxidation of the polyunsaturated fatty acid or derivative to a greater extent than a standard type IIa gelatin capsule. In another embodiment, the capsule contains no chemically modified gelatin, for example succinated, succinylated, pthalated, carbanylated and/or phenol carbanylated gelatin.

[0029] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell as described herein and having a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein upon storage of the composition at 23 °C and 50% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the ultra-pure EPA has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0030] The "baseline peroxide value" and "second peroxide values" can be measured in any suitable manner, for example by using a U.S. or PhEur or JP compendial method. Typically, a plurality of encapsulated EPA compositions are provided, each composition containing EPA having been encapsulated at substantially the same time. A first sampling of 1 or more capsules from the plurality is provided, the capsules are opened and peroxide value of the EPA is measured substantially immediately thereafter, providing an average baseline peroxide value. At substantially the same time, a second sampling of 1 or more capsules from the plurality are provided and are placed under desired storage conditions for a desired time period. At the end of the desired time period, the capsules are opened and peroxide value of the EPA is measured substantially immediately thereafter, providing an average second peroxide value. The baseline and second peroxide values can then be compared. In one embodiment, the "baseline peroxide value" and "second peroxide value" are determined using a plurality of encapsulated EPA dosage units wherein each dosage unit was encapsulated (i.e. the EPA filled and sealed into capsules) within a same 60 day period, same 30 day period, a same 20 day period, a same 10 day period, a same 5 day period or a same 1 day period.

[0031] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell as described herein and having a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein upon storage of the composition at 25 °C and 60% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0032] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell as described herein and having a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein upon storage of the composition at 30 °C and 65% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0033] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell as described herein and having a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein upon storage of the composition at 40 °C and 75% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0034] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell and having a baseline

peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of not less than 1.75:1 and wherein upon storage of the composition at 23 °C and 50% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0035] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell and having a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of not less than 1.75:1 and wherein upon storage of the composition at 25 °C and 60% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0036] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell and having a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of not less than 1.75:1 and wherein upon storage of the composition at 30 °C and 65% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0037] In another example, the disclosure provides a pharmaceutical composition comprising

EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell and having a baseline peroxide value not greater than about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of not less than 1.75:1 and wherein upon storage of the composition at 40 °C and 75% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition has a second peroxide value not greater than about 25 Meq/kg, about 24 Meq/kg, about 23 Meq/kg, about 22 Meq/kg, about 21 Meq/kg, about 20 Meq/kg, about 19 Meq/kg, about 18 Meq/kg, about 17 Meq/kg, about 16 Meq/kg, about 15 Meq/kg, about 14 Meq/kg, about 13 Meq/kg, about 12 Meq/kg, about 11 Meq/kg, about 10 Meq/kg, about 9 Meq/kg, about 8 Meq/kg, about 7 Meq/kg, about 6 Meq/kg, about 5 Meq/kg, about 4 Meq/kg, about 3 Meq/kg or about 2 Meq/kg.

[0038] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount (*i.e.* initial amount) of EPA or E-EPA, wherein upon storage of the composition at 23 °C and 50% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition contains at least about 97%, about 98%, about 99%, about 99.5%, about 99.7%, about 99.9% or substantially all or 100% of the labeled amount of EPA or E-EPA, by weight.

[0039] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount (*i.e.* initial amount) of EPA or E-EPA, wherein upon storage of the composition at 25 °C and 60% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition contains at least about 97%, about 98%, about 99%, about 99.5%, about 99.7%, about 99.9% or substantially all or 100% of the labeled amount of EPA or E-EPA, by weight.

[0040] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein upon storage of the composition at 30 °C and 65% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition contains at least about 97%, about 98%, about 99%, about 99.5%, about 99.7%, about 99.9%, substantially all or 100% of the labeled amount of EPA or E-EPA, by weight.

[0041] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA, wherein upon storage of the composition at 40 °C and 75% RH for a period about 1, about 2,

about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition contains at least about 97%, about 98%, about 99%, about 99.5%, about 99.7%, about 99.8%, about 99.9%, substantially all or 100% of the labeled amount of EPA or E-EPA, by weight.

[0042] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA containing a labeled amount of EPA or E-EPA, wherein upon storage of the composition at 23 °C and 50% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition contains not more than about 0.5%, not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product. The term "degradation product" in the present context means "an impurity resulting from a chemical change in the composition brought about during manufacture and/or storage of the composition by the effect of, for example, light, temperature, pH, water or by reaction with an excipient and/or the immediate container closure system." The term "specified degradation product in the present context means "a degradation product, either identified or unidentified, that is individually listed and limited with a specific acceptance criterion in the product specification" for a particular product.

[0043] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein upon storage of the composition at 25 °C and 60% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5%, not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0044] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein upon storage of the composition at 30 °C and 65% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0045] In another example, the disclosure provides a pharmaceutical composition comprising

encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein upon storage of the composition at 40 °C and 75% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0046] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein the capsule comprises a film-forming material, a hygroscopic plasticizer and a non-hygroscopic plasticizer and upon storage of the composition at 23 °C and 50% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0047] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA, wherein the capsule comprises a film-forming material, a hygroscopic plasticizer and a non-hygroscopic plasticizer and upon storage of the composition at 25 °C and 60% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0048] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA, wherein the capsule comprises a film-forming material, a hygroscopic plasticizer and a non-hygroscopic plasticizer and upon storage of the composition at 30 °C and 65% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or

specified degradation product.

[0049] In another example, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein the capsule comprises a film-forming material, a hygroscopic plasticizer and a non-hygroscopic plasticizer and upon storage of the composition at 40 °C and 75% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0050] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of about 2:5:1 to about 10:1 and upon storage of the composition at 23 °C and 50% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, the composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0051] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated EPA (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of about 2:5:1 to about 10:1 and upon storage of the composition at 25 °C and 60% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0052] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of about 2:5:1 to about 10:1 and upon storage of the composition at 30 °C and 65% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19,

about 20, about 21, about 22, about 23 or about 24 months, said composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0053] In another example, the disclosure provides a pharmaceutical composition comprising encapsulated (e.g. E-EPA or ultra pure E-EPA) containing a labeled amount of EPA or E-EPA, wherein the capsule comprises a film-forming material and a plasticizer in a weight ratio of about 2:5:1 to about 10:1 and upon storage of the composition at 40 °C and 75% RH for a period about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, about 20, about 21, about 22, about 23 or about 24 months, said composition contains not more than about 0.5% (by weight of the labeled EPA or E-EPA), not more than about 0.25%, not more than about 0.15%, not more than about 0.125%, not more than about 0.1%, not more than about 0.075%, not more than about 0.05% or substantially no degradation product and/or specified degradation product.

[0054] In another example, the present disclosure provides a pharmaceutical composition comprising about 0.5 g to about 1.5 g of EPA (e.g. E-EPA or ultra pure E-EPA) having a labeled amount of EPA or E-EPA encapsulated in a pharmaceutical capsule, wherein upon storage at 15 °C to 30 °C for a period of about 6 months, 12 months, 18 months, 24 months, 30 months, or 36 months, at least about 97%, about 98%, about 99%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9% or substantially all of the labeled amount of EPA is still present in the composition. In a related example, the composition has not reached its labeled expiration date during said storage period.

[0055] In various embodiments, capsule shells suitable for use in the present invention comprise one or more film-forming materials, one or more plasticizers and optionally a solvent (*e.g.* water). According to the invention, the film-forming material comprises gelatin. In another example, the plasticizer comprises a hygroscopic and/or non-hygroscopic plasticizer. In one embodiment, the capsule shell comprises a film-forming material (particularly gelatin), a hygroscopic plasticizer, a non-hygroscopic plasticizer and a solvent.

[0056] In another embodiment, the capsule shell comprises about 30% to about 70% or about 40% to about 65%, by weight, of a film-forming material, about 15% to about 40% or about 20% to about 35%, by weight, of one or more plasticizers, and about 3% to about 15% or about 5% to about 10%, by weight, solvent such as water. Optionally, the capsules may also contain additives such as colorants, flavorants, preservatives, disintegrants, surfactants, fragrances, sweeteners, *etc.*

[0057] Capsules of the invention comprise a film-forming material, in particular gelatin. Gelatin is typically manufactured from animal byproducts that contain collagen, for example in the bones, skin, and connective tissue. Methods of producing gelatin from animal byproducts are

well-known in the art. In various embodiments, the gelatin may be alkali-treated gelatin, acid-treated gelatin, chemically modified gelatin, or mixtures thereof. Methods to produce alkali-treated gelatin, acid-treated gelatin, and chemically modified gelatin are known in the art and are described, for example in Nakamura et al., U.S. 2003/0195246.

[0058] The film-forming material may also comprise, for example, non-animal based hydrocolloids such as carrageenan, alkylated or hydroxyalkylated cellulose ethers, starch, alpha-starch, hydroxyalkyl starch, sodiuim alginate, sodium salt of a gelatin copolymer and acrylic acid.

[0059] The film-forming material can comprise a 20:80 to about 80:20, by weight, mixture, for example a 60:40, by weight mixture of hydroxypropyl methyl cellulose and polyvinyl alcohol (*e.g.* about 70% to about 90%, for example about 88.0% saponified; and about 30 to about 50, for example about 45.0 centipoise viscosity). In another embodiment, the film-forming material can comprise a 20:80 to about 80:20, by weight, mixture, for example a 60:40, by weight, mixture of hydroxyethyl cellulose and polyvinyl alcohol (*e.g.* about 70% to about 99.9%, for example about 98.5% saponified; and about 2 to about 30, for example about 5.5 centipoise viscosity).

[0060] A suitable capsule shell may further comprise an elasticity reducing gel extender as part of the film-forming material. An elasticity reducing gel extender can comprise starch, starch derivatives such as high amylose starch, oxidized starch, esterified starch, acid-thinned starch, etherified starch, hydrolyzed starch, hydrolyzed and hydrogenated starch, enzyme treated starch, and modified celluloses or other natural or modified natural biopolymers such as bacterial polysaccharides, vegetable gums, or other exudates including alginates, carrageenans, guar gum, gum arabic, gum ghatti, gum karaya, gum tragacanth, pectins, tamarind gum, xanthan gum, and dextrans as well as synthetic polymers such as carbon chain polymers of the vinyl and acrylic types as well as heterochains of the polyoxide and polyamine types including polyethylene oxide, polypropylene oxide, polyoxymethylene, polytrimethylene oxide, block copolymers of ethylene oxide, block copolymers of polyethylene oxide, polyvinyl methyl ether, polyethylene imine, polyacrylic acid, polyacrylamide, polymethacrylic acid, polymethacrylamide, poly(N,N-Dimethylacrylamide), poly(N-Isopropylacrylamide), poly(N-Acrylylglycinamide), poly(N-Methyacrylyglycinamide), acrylic copolymers, polyvinyl alcohol polyvinylacetate, polyvinyl acetate-co-vinyl alcohol, polyvinylpyrrolidone, N-Methylpyrrolidone, N-Ethylpyrrolidone, N-Vinylpyrrolidone, sarcosine anhydride, polyvinyloxazolindone, and polyvinylmethyloxazolidone. The starch or other elasticity reducing gel extender may be added into the formulation in amounts ranging from about 8% to about 30% by weight , for example about 10% to about 16%, by weight.

[0061] Capsule shells suitable for use in various examples of the disclosure can comprise one or more plasticizers, for example hygroscopic and/or non-hygroscopic plasticizers. Capsule shells of the invention comprise hygroscopic and non-hygroscopic plasticizers. Non-limiting examples of suitable hygroscopic plasticizers include glycerin, sorbitol and alkylene glycols (*e.g.*, propylene glycol and low molecular weight polyethylene glycols). Non-limiting examples

of suitable non-hygroscopic plasticizers include partially dehydrated hydrogenated glucose syrup, maltitol, maltose, lactitol, xylitol, erythritol and polyethylene glycols of average molecular weights from about 400 to about 6000.

[0062] In one embodiment, a capsule shell suitable for use in a composition of the invention has a hygroscopic plasticizer to non-hygroscopic plasticizer weight ratio of about 1:1 to about 8:1, about 2:1 to about 6:1, about 3:1 to about 5:1, for example about 4:1, about 4.25:1, about 4.5:1 or about 4.75:1.

[0063] In another embodiment, a capsule shell suitable for use in a composition of the invention has a gelatin to glycerol weight ratio of about 2:5:1 to about 10:1, about 3.5:1 to about 9:1, about 4:1 to about 8:1, or about 5:1 to about 7:1, for example at least about 2.6:1, at least about 2.7:1, at least about 2.8:1, at least about 2.9:1, at least about 3:1, at least about 3.1:1, at least about 3.2:1, at least about 3.3:1, at least about 3.4:1, at least about 3.5:1, at least about 3.6:1, at least about 3.7:1, at least about 3.8:1, at least about 3.9:1, at least about 4.0:1, at least about 4.1:1, at least about 4.2:1, at least about 4.3:1, at least about 4.4:1, at least about 4.5:1, at least about 4.6:1, at least about 4.7:1, at least about 4.8:1, at least about 4.9:1, at least about 5.0:1, at least about 5.1:1, or at least about 5.2:1.

[0064] In another embodiment, a suitable capsule shell has a film-forming material (*e.g.* gelatin) to total plasticizer weight ratio of about 1.75 to about 5, about 1.78 to about 3, or about 1.8 to about 2.5, for example at least about 1.76, at least about 1.77, at least about 1.78, at least about 1.79, at least about 1.8, at least about 1.81, at least about 1.82, at least about 1.83, or at least about 1.84.

[0065] In another embodiment, the capsule shell has: (1) a gelatin to glycerol weight ratio of about 2:5:1 to about 10:1, about 3.5:1 to about 9:1, about 4:1 to about 8:1, or about 5:1 to about 7:1, for example at least about 2.6:1, at least about 2.7:1, at least about 2.8:1, at least about 2.9:1, at least about 3:1, at least about 3.1:1, at least about 3.2:1, at least about 3.3:1, at least about 3.4:1, at least about 3.5:1, at least about 3.6:1, at least about 3.7:1, at least about 3.8:1, at least about 3.9:1, at least about 4.0:1, at least about 4.1:1, at least about 4.2:1, at least about 4.3:1, at least about 4.4:1, at least about 4.5:1, at least about 4.6:1, at least about 4.7:1, at least about 4.8:1, at least about 4.9:1, at least about 5.0:1, at least about 5.1:1, or at least about 5.2:1; and/or (2) a gelatin to total plasticizer weight ratio of about 1.75:1 to about 5:1, about 1.78:1 to about 3:1, or about 1.8:1 to about 2.5:1, for example at least about 1.76:1, at least about 1.77:1, at least about 1.78:1, at least about 1.79:1, at least about 1.8:1, at least about 1.81, at least about 1.82, at least about 1.83, or at least about 1.84.

[0066] In one embodiment, the capsule shell comprises one or more of: gelatin in an amount of about 50% to about 70%; glycerol in an amount of about 5% to about 15%; sorbitol in an amount of about 15% to about 25%; and/or maltitol in an amount of about 3% to about 10%, by weight of the non-aqueous components. Such a capsule can further comprise about 2% to about 16% by weight of a solvent such as water.

[0067] In another embodiment, a capsule shell suitable for use in compositions of the present invention can be prepared using a gel mass comprising about 40% to about 50% gelatin, about 2% to about 12% glycerol, about 10% to about 20% sorbitol solution, about 2% to about 10% maltitol syrup, and about 20% to about 35% water, by weight. In one embodiment, a capsule shell suitable for us in a composition of the present invention can be prepared using a gel mass comprising about 45% gelatin by weight, about 7% glycerol by weight, about 17% sorbitol solution (*e.g.* 30% water) by weight, about 6% maltitol syrup (e.g. 15% - 32% water) by weight, and about 25% water by weight. Capsules prepared from such a gel mass can be dried to about 2% to about 12% final moisture content. Capsules prepared by such a process that contain EPA (e.g. E-EPA or ultra pure E-EPA), and methods of using the same in the treatment of cardiovascular-related diseases represent further examples of the disclosure. Capsule compositions as described herein can further comprise coatings, for example enteric polymer or wax coatings.

[0068] In one embodiment, a composition of the invention provides a relatively rapid dissolution profile yet still maintains excellent stability of the encapsulated material (e.g. EPA). In a related embodiment, a composition of the invention has a dissolution profile (as measured by Rotating Dialysis Cell Dissolution (RDC) Apparatus under the conditions set forth herein below) of one or more of the following: (1) at least about 20%, at least about 23% or at least about 25% of E-EPA is dissolved by 10 minutes; (2) at least about 45%, at least about 50% or at least about 55% of E-EPA is dissolved by 30 minutes; (3) at least about 80%, at least about 82%, at least about 85% or at least about 87% of E-EPA is dissolved by 60 minutes; and/or (4) at least about 95%, at least about 97% or 100% of E-EPA is dissolved by 100 minutes. In a related embodiment, the fill material still retains the stability/peroxide values as set forth throughout this specification.

[0069] In another embodiment, a composition of the invention provides a relatively short T_{max} yet still maintains excellent stability of the encapsulated material (e.g. EPA). In a related embodiment, a composition of the invention, upon administration to a subject, exhibits an EPA T_{max} less than 6 hours, less than 5.8 hours, less than 5.6 hours, less than 5.4 hours or less than 5.2 hours, for example about 4.8 to about 5.2 hours. In a related embodiment, the fill material still retains the stability/peroxide values as set forth throughout this specification.

[0070] In one example, a method for treatment and/or prevention of a cardiovascular-related disease using a composition as described herein is provided. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (*i.e.* arteries and veins) or any symptom thereof. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (*i.e.* arteries and veins) or any symptom thereof, or any disease or condition that causes or contributes to a cardiovascular disease." Non-limiting examples of cardiovascular-related diseases include acute cardiac ischemic events, acute myocardial infarction , angina, angina pectoris, arrhythmia, atrial fibrulation, atherosclerosis, arterial fibrillation, cardiac insufficiency, cardiovascular disease, chronic heart failure, chronic stable angina, congestive heart failure, coronary artery disease, coronary heart disease, deep vein thrombosis, diabetes, diabetes mellitus, diabetic neuropathy, diastolic

dysfunction in subjects with diabetes mellitus, edema, essential hypertension , eventual pulmonary embolism, fatty liver disease, heart disease, heart failure, homozygous familial hypercholesterolemia (HoFH), homozygous familial sitosterolemia, hypercholesterolemia, hyperlipidemia, hyperlipidemia in HIV positive subjects, hypertension, hypertriglyceridemia, ischemic complications in unstable angina and myocardial infarction, low blood pressure, metabolic syndrome, mixed dyslipidemia, moderate to mild heart failure, myocardial infarction, obesity management, paroxysmal atrial/arterial fibrillation/fibrulation/flutter, paroxysmal supraventricular tachycardias (PSVT), particularly severe or rapid onset edema, platelet aggregation, primary hypercholesterolemia, primary hyperlipidemia, pulmonary arterial hypertension, pulmonary hypertension, recurrent hemodynamically unstable ventricular tachycardia (VT), recurrent ventricular arrhythmias, recurrent ventricular fibrillation (VF), ruptured aneurysm, sitisterolemia, stroke, supraventricular tachycardia, symptomatic atrial fibrillation/flutter, tachycardia, type-II diabetes, vascular disease, venous thromboembolism, ventricular arrhythmias, and other cardiovascular events.

[0071] The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

[0072] In one example, the present disclosure provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another example, the subject or subject group has hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia and/or very high triglycerides.

[0073] In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of at least about 300 mg/dl, at least about 400 mg/dl, at least about 500 mg/dl, at least about 600 mg/dl, at least about 700 mg/dl, at least about 800 mg/dl, at least about 900 mg/dl, at least about 1000 mg/dl, at least about 1100 mg/dl, at least about 1200 mg/dl, at least about 1300 mg/dl, at least about 1400 mg/dl, or at least about 1500 mg/dl, for example about 400 mg/dl to about 2500 mg/dl, about 450 mg/dl to about 2000 mg/dl or about 500 mg/dl to about 1500 mg/dl.

[0074] In another example, the subject or subject group being treated in accordance with methods of the disclosure has previously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-C levels and/or non-HDL-C levels. In one such example, Lovaza® therapy is discontinued and replaced by a method of the present disclosure.

[0075] In another example, the subject or subject group being treated in accordance with methods of the disclosure exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another example, the subject or subject group being treated in accordance with methods of the disclosure exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such example, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

[0076] In another example, the subject or subject group being treated in accordance with methods of the disclosure exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

[0077] In another example, the subject or subject group being treated in accordance with methods of the disclosure exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 µg/ml, not greater than about 60 µg/ml, not greater than about 50 µg/ml, not greater than about 40 µg/ml, not greater than about 30 µg/ml, or not greater than about 25 µg/ml.

[0078] In another example, methods of the present disclosure comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another example, methods of the disclosure comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dl to about 400 mg/dl, for example at least about 210 mg/dl, at least about 220 mg/dl, at least about 230 mg/dl, at least about 240 mg/dl, at least about 250 mg/dl, at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl, at least about 290 mg/dl, or at least about 300 mg/dl; baseline total cholesterol value of about 250 mg/dl to about 400 mg/dl, for example at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl or at least about 290 mg/dl; baseline vLDL-C value of about 140 mg/dl to about 200 mg/dl, for example at least about 150 mg/dl, at least about 160 mg/dl, at least about 170 mg/dl, at least about 180 mg/dl or at least about 190 mg/dl; baseline HDL-C value of about 10 to about 60 mg/dl, for example not more than about 40 mg/ dl, not more than about 35 mg/dl, not more than about 30 mg/dl, not more than about 25 mg/dl, not more than about 20 mg/dl, or not more than about 15 mg/dl; and/or baseline LDL-C value of about 50 to about 300 mg/dl, for example not less than about 100 mg/dl, not less than about 90 mg/dl, not less than about 80 mg/dl, not less than about 70 mg/dl, not less than about 60 mg/dl or not less than about 50 mg/dl.

[0079] In one embodiment, compositions of the invention are packaged in blister packs. In another embodiment, the blister packs comprise PCTFE (for example 50µ) laminated with water based adhesive to clear PVC (for example 190µ) which are heat sealed to aluminum foil).

[0080] In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

1. (a) reduced triglyceride levels compared to baseline or a placebo arm;
2. (b) reduced Apo B levels compared to baseline or a placebo arm;
3. (c) increased HDL-C levels compared to baseline or a placebo arm;
4. (d) no increase in LDL-C levels compared to baseline or a placebo arm;
5. (e) a reduction in LDL-C levels compared to baseline or a placebo arm;
6. (f) a reduction in non-HDL-C levels compared to baseline or a placebo arm;
7. (g) a reduction in vLDL levels compared to baseline or a placebo arm;
8. (h) an increase in apo A-I levels compared to baseline or a placebo arm;
9. (i) an increase in apo A-I/apo B ratio compared to baseline or a placebo arm;
10. (j) a reduction in lipoprotein A levels compared to baseline or a placebo arm;
11. (k) a reduction in LDL particle number compared to baseline or a placebo arm;
12. (l) an increase in mean LDL size compared to baseline or a placebo arm;
13. (m) a reduction in remnant-like particle cholesterol compared to baseline or a placebo arm;
14. (n) a reduction in oxidized LDL compared to baseline or a placebo arm;
15. (o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline or a placebo arm;
16. (p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline or a placebo arm;
17. (q) a reduction in homeostasis model insulin resistance compared to baseline or a placebo arm;
18. (r) a reduction in lipoprotein associated phospholipase A2 compared to baseline or a placebo arm;
19. (s) a reduction in intracellular adhesion molecule-1 compared to baseline or a placebo arm;
20. (t) a reduction in interleukin-6 compared to baseline or a placebo arm;
21. (u) a reduction in plasminogen activator inhibitor-1 compared to baseline or a placebo arm;
22. (v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline or a placebo arm;
23. (w) an increase in serum phospholipid EPA compared to baseline or a placebo arm;
24. (x) an increase in red blood cell membrane EPA compared to baseline or a placebo arm; and/or

25. (y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline or a placebo arm.

[0081] In one example, methods of the present disclosure comprise measuring baseline levels of one or more markers set forth in (a) - (y) above prior to dosing the subject or subject group. In another example, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) - (y) are determined, and subsequently taking an additional measurement of said one or more markers.

[0082] In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a) - (y) described immediately above.

[0083] In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

1. (a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;
2. (b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;
3. (c) substantially no change, no change or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;

4. (d) a less than 60% increase, less than 50% increase, less than 40% increase, less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;
5. (e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline or a placebo arm;
6. (f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
7. (g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
8. (h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
9. (i) a reduction in lipoprotein(a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
10. (j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
11. (k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
12. (l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
13. (m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual

% change or median % change) compared to baseline or a placebo arm;

14. (n) substantially no change, no change or a reduction in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
15. (o) substantially no change, no change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline or a placebo arm;
16. (p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
17. (q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
18. (r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
19. (s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
20. (t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;
21. (u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline or a placebo arm;
22. (v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline or a placebo arm;

23. (w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline or a placebo arm;
24. (x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline or a placebo arm; and/or
25. (y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline or a placebo arm.

[0084] In one example, methods of the present disclosure comprise measuring baseline levels of one or more markers set forth in (a) - (y) prior to dosing the subject or subject group. In another example, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) - (y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

[0085] In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 25 of outcomes (a) - (y) described immediately above.

[0086] Parameters (a) - (y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from

serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-2 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6th Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

[0087] In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

[0088] In another example, the present disclosure provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related example, the present disclosure provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

[0089] In another example, the present disclosure provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

[0090] In another example, the present disclosure provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

[0091] In another example, the present disclosure provides a method of treating or preventing very high serum triglyceride levels (e.g. Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

[0092] In another example, the present disclosure provides a method of treating subjects having very high serum triglyceride levels (*e.g.* greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

[0093] In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg,

about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

[0094] In another example, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

EXAMPLES

[0095] The following examples are for illustrative purposes only and should not be construed as limiting the invention in any manner.

Example 1

[0096] A Test Composition (TC) was prepared comprising ultra-pure Ethyl-EPA (>96% E-EPA, ~3% related fatty acid substances (no DHA), and ~ 0.2% alpha tocopherol) filled into soft gelatin capsule shells (~500 mg fill weight per capsule) prepared from a gel comprising gelatin (~44%), glycerol (~7%), sorbitol solution (~17%), maltitol solution, gelatin and purified water. A Comparative Composition (CC) was made comprising the same fill as the Test Composition but filled into Type IIa Capsules made from a gel comprising of glycerol (~20%), gelatin (43.4%) and water (~36.6%).

[0097] Test Compositions and Comparative Compositions were then placed in polybags which were sealed and stored at either 25 °C/60% RH or 30 °C/65% RH for a period of 1, 3, or 6 months. At the end of storage, capsules were opened and peroxide value of the fill material was analyzed. Results are shown in Table 1 (average of capsules from three different batches).

Table 1. Peroxide Values (Meq/kg) Upon Storage.

Composition	Baseline	1 Month	3 Month	6 Month
	Storage at 25 °C/60% RH			
TC	1.6	-	3.2	3.4
CC	1.9	-	3.4	9.6
	Storage at 30 °C/65% RH			
TC	1.6	2.0	3.6	4.8
CC	1.8	1.9	3.5	12.5

[0098] As is seen in Table 1, the Test Composition fill material exhibited much lower peroxide values after 6 months of storage under both sets of storage conditions. No significant differences were observed between the Test Composition and Comparative Composition fill material in terms of potency of EPA-E and related substances throughout the duration of the study.

Example 2

[0099] Test Compositions and Comparative Compositions of Example 1 were prepared and packaged in blister packaging (50µ PCTFE laminated with water based adhesive to 190µ clear PVC and heat sealed to aluminum foil). Packaged Test Compositions and Comparative Compositions were then stored at either 25 °C/60% RH or 40 °C/70% RH for a period of 1, 3, 6, 12 or 36 months. At the end of storage, capsules were opened and the peroxide values of the fill contents analyzed as shown in Table 2 (average of the three batches).

Table 2. Peroxide Values (Meq/kg) Upon Storage

	Baseline	1 Mo.	3 Mo.	6 Mo.	9 Mo.	12 Mo.
	Storage at 25 °C/60% RH					
TC	2.5	--	1.1	2.1	2.2	5.4
CC	2.6	--	5.1	8.3	9.7	11.1
	Storage at 40 °C/75% RH					
TC	2.5	2.1	3.2	4.9	--	--
CC	2.6	3.4	10.6	18.8	--	--

[0100] As is seen in Table 2, the Test Composition exhibited much lower peroxide values after 3, 6, 9 and 12 months of storage at 25 °C/60% RH and after 1, 3 and 6 months of storage at 40 °C/75% RH as compared to the Comparative Compositions.

[0101] At 40 °C, the Test Composition showed an average decrease in E-EPA potency of 0.30% per month whereas the Comparative Compositions showed an average decrease in E-EPA potency of 0.44% per month. However, similar results were not obtained with the same batches in Example 1 (not stored in blister packages). Additionally, the related substances measurements did not show any concomitant increase suggesting normal analytic variation may be responsible.

[0102] When the peroxide values were forced to linear trendlines, average slope values between the Test Compositions in Experiment 1 (no blister packaging) and Experiment 2 (blister packaging) were similar indicating that the packaging is likely not responsible for prevention of oxidation.

Table 3. Peroxide Value: Linear Slope Comparison Between Example 1 and Example 2

	Test Composition		**Comparative Composition**	
Storage Conditions	Slope (Meq/kg/mo.)		Slope (Meq/kg/mo.)	
	Example 1	Example 2	Example 1	Example 2
25 °C/60% RH	0.33	0.35	1.45	1.03
40 °C/75% RH	0.56	0.66	1.81	3.00

Example 3

[0103] A dissolution test was performed on capsules of Example 1 containing 500 mg E-EPA using the Rotating Dialysis Cell method set forth in Yamazaki et al., Dissolution tests by RDC method for soft gelatin capsules containing ethyl icosapentate, Pharmaceutical Technology Japan, 15: 595-603 (1999). Conditions were as set forth below:

RDC Cell:	PharmaTest
Paddle speed:	100rpm
Temperature:	37°C
Filter:	Millipore hydrophobic filter sheets
Inner media:	JP pH 1.2 disintegration media
Outer Media:	Absolute Ethanol
Samples:	5ml taken at 10, 20, 30, 40, 60, 100 and 120 minutes

[0104] The samples were analyzed against a reference standard prepared in ethanol at

0.5mg/ml, the amount of product dissolved at each time point was then calculated. A good dissolution profile was obtained with a Q_{85} of approximately 60 minutes and a profile very similar to that generated by Yamazaki (JP data; succinated gelatin capsules). Dissolution profile of the inventive capsule composition was also evaluated by the paddle method in media containing buffer, SDS and IPA (100 rpm paddle speed, 1000ml, 37 °C). Samples were removed at intervals and analyzed against a standard solution (9.5ml/ml in methanol) by HPCL. All data are shown in Figure 1.

Example 4

[0105] Bioavailability data were obtained for a capsule shell according to Example 1 containing 500 mg E-EPA (AMR101) and were compared against reported by Yamazaki data for 300 mg Epadel capsules (succinated gelatin; Comparitor 1 and Comparitor 2). Tmax data are shown in Table 4 together with dissolution percentage at 60 min. Full bioavailability profiles for EPA succinated capsules and AMR101 capsules are shown in Figures 2 and 3, respectively.

Table 4. Dissolution and Tmax

	Dissolution at 60 min (%)	**T_{max} (hrs)**
Comparitor 11	77	6
Comparitor 2[2]	75	6
AMR101[3]	87	5

[1]Capsule shell = 220 mg; contents = 323 mg.
[2]Capsule shell = 134 mg; contents = 327 mg.
[3]Mean of three batches using RDC and pH 1.2.

[0106] As can be seen from Table 4, AMR101 exhibited greater E-EPA dissolution by 60 minutes, and had a shorter T_{max} than was reported for Epadel present in succinated gelatin capsules.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US20060134178A [0001]
- US6193999B [0001]
- US20030195246A [0057]

Non-patent literature cited in the description

- Tietz Fundamentals of Clinical ChemistryWB Saunders Company [0086]
- **YAMAZAKI et al.**Dissolution tests by RDC method for soft gelatin capsules containing ethyl icosapentatePharmaceutical Technology, 1999, vol. 15, 595-603 [0103]

Patentkrav

1. Farmaceutisk sammensætning der omfatter mindst 95 % eicosapentaensyre (EPA), som er indesluttet i en kapselskal, hvor:

a) den farmaceutiske sammensætning har en basislinje-peroxidværdi, der ikke er større end 5 Meq/kg, og ved opbevaring af den farmaceutiske sammensætning ved 25 °C og 60 % RF i en periode på 6 måneder har den farmaceutiske sammensætning en anden peroxidværdi, der ikke er større end 8 Meq/kg,

b) kapselskallen omfatter: (i) et filmdannende materiale der omfatter gelatine, men i det væsentlige ingen succineret gelatine,
(ii) et hygroskopisk blødgøringsmiddel der omfatter glycerol og
(iii) et ikke-hygroskopisk blødgøringsmiddel som er valgt blandt: maltitol, lactitol, xylitol, hydrogeneret stivelseshydrolysat og glucosesirup,

hvilket hygroskopiske blødgøringsmiddel og ikke-hygroskopiske blødgøringsmiddel er til stede i et vægtforhold på ca. 2 : 1 til ca. 6 : 1.

2. Farmaceutisk sammensætning ifølge krav 1, hvor EPA er ethyl-eicosapentaenoat (ethyl-EPA), eventuelt hvor:

a) ethyl-EPA indeholder mindre end ca. 1 % af en hvilken som helst individuel fedtsyre bortset fra ethyl-EPA; eller

b) ethyl-EPA indeholder mindre end ca. 0,5 % af en hvilken som helst individuel fedtsyre bortset fra ethyl-EPA; eller

c) ethyl-EPA indeholder mindre end ca. 0,3 % docosahexaensyre (DHA), hvis nogen, eventuelt hvor ethyl-EPA i det væsentlige ikke indeholder DHA.

3. Farmaceutisk sammensætning ifølge krav 1, hvor ethyl-EPA omfatter ca. 0,1 til ca. 1 vægt-% af en antioxidant, hvilken antioxidant eventuelt er tocopherol.

4. Farmaceutisk sammensætning ifølge krav 1, hvor:

a) ved opbevaring af den farmaceutiske sammensætning ved 25 °C og 60 % RF i en periode på 6 måneder EPA har en anden peroxidværdi, der ikke er større end 7 Meq/kg eller 6 Meq/kg; eller

b) EPA har ved opbevaring af den farmaceutiske sammensætning ved 30 °C og 65 % RF i en periode på 6 måneder en anden peroxidværdi, der ikke er større end 12 Meq/kg, ikke større end 10 Meq/kg eller ikke større end 6 Meq/kg.

5. Farmaceutisk sammensætning ifølge krav 1, hvor det filmdannende materiale omfatter glycerol og gelatine.

6. Farmaceutisk sammensætning der omfatter mindst ca. 95 % ethyl-eicosapentaenoat (ethyl-EPA), som er indesluttet i en kapselskal, hvor:

a) ethyl-EPA har en basislinje-peroxidværdi der ikke er større end 5 Meq/kg, og ved opbevaring af den farmaceutiske sammensætning ved 30 °C og 65 % RF i en periode på 6 måneder har ethyl-EPA en anden peroxidværdi, der ikke er større end 5 Meq/kg, hvilken kapselskal ikke indeholder nogen kemisk-modificeret gelatine;

b) kapselskallen omfatter: (i) et filmdannende materiale der omfatter gelatine i en mængde på 50 til 70 vægt-% af de ikke-vandige komponenter, (ii) et hygroskopisk blødgøringsmiddel der omfatter glycerin i en mængde på 5 til 15 vægt-% af de ikke-vandige komponenter og sorbitol i en mængde på 15 til 25 vægt-% af de ikke-vandige komponenter, og (iii) et ikke-hygroskopisk blødgøringsmiddel der omfatter maltitol i en mængde på 3 til 10 vægt-% af de ikke-vandige komponenter.

7. Farmaceutisk sammensætning der omfatter mindst ca. 95 % ethyl-eicosapentaenoat (ethyl-EPA), som er indkapslet i en kapselskal, der omfatter ikke-kemisk-modificeret gelatine, hvilken kapselskal omfatter:
et hygroskopisk blødgøringsmiddel der omfatter glycerol og sorbitol, og
et ikke-hygroskopisk blødgøringsmiddel der omfatter maltitol,
hvilken kapselskal har et vægtforhold mellem gelatine og hygroskopisk blødgøringsmiddel på ca. 4 : 1 til ca. 8 : 1 og et vægtforhold mellem hygroskopisk

blødgøringsmiddel og ikke-hygroskopisk blødgøringsmiddel på ca. 3 : 1 til ca. 5 : 1 og gelatine:glycerol-forholdet er mindst 5,1 : 1.

8. Farmaceutisk sammensætning ifølge krav 7, hvor:

a) den farmaceutiske sammensætning har en basislinje-peroxidværdi der ikke er større end 5 Meq/kg, og ved opbevaring af den farmaceutiske sammensætning ved 25 °C og 60 % RF i en periode på 6 måneder har den farmaceutiske sammensætning en anden peroxidværdi, der ikke er større end 8 Meq/kg; eller

b) den farmaceutiske sammensætning har en basislinje-peroxidværdi, der ikke er større end 5 Meq/kg, og ved opbevaring af sammensætningen ved 25 °C og 60 % RF i en periode på 6 måneder har ethyl-EPA en anden peroxidværdi, der ikke er større end 5 Meq/kg.

9. Sammensætning til anvendelse ved behandling eller forebyggelse af en kardiovaskulær-relateret sygdom hos et individ med behov deraf, hvor sammensætningen omfatter en terapeutisk effektiv mængde af den farmaceutiske sammensætning ifølge krav 1.

10. Sammensætning til anvendelsen ifølge krav 9, hvor den kardiovaskulær-relaterede sygdom er valgt blandt: akutte iskæmiske hændelser, akut myokardieinfarkt, angina, angina pectoris, arytmi, atrieflimren, aterosklerose, hjerteinsufficiens, kardiovaskulær sygdom, kronisk hjertesvigt , kronisk stabil angina, kongestiv hjertesvigt, koronararteriesygdom, koronar hjertesygdom, dyb venetrombose, diabetes, diabetes mellitus, diabetisk neuropati, diastolisk dysfunktion hos personer med diabetes mellitus, ødem, essentiel hypertension, eventuel lungeemboli, fedtleversygdom, hjertesygdom, hjertesvigt, homozygot familiær hyperkolesterolæmi (HoFH), homozygot familiær sitosterolæmi, hyperkolesterolæmi, hyperlipidæmi, hypertension, hypertriglyceridæmi, iskæmisk komplikationer i ustabil angina og myokardieinfarkt, lavt blodtryk, metabolisk syndrom, blandet dyslipidæmi, moderat til mild hjertesvigt, myokardie infarkt, blodpladeaggregering, primær hyperkolesterolæmi, primær hyperlipidæmi, pulmonal arteriel hypertension, pulmonal hypertension, tilbagevendende hæmodynamisk ustabil ventrikulær takykardi

(VT), tilbagevendende ventrikulær arytmi, tilbagevendende ventrikelflimren (VF), brudt aneurisme, sitosterolæmi, slagtilfælde, supraventrikulær takykardi, symptomatisk atrieflimren/flagren, takykardi, type II diabetes, vaskulær sygdom, venøs tromboembolisme og ventrikulær arytmi, eventuelt hvor den kardiovaskulær-relaterede sygdom er hypertriglyceridæmi.

11. Farmaceutisk sammensætning ifølge krav 7, hvor vægtforholdet mellem gelatine og glycerol er mindst 5,2 : 1.

DRAWINGS

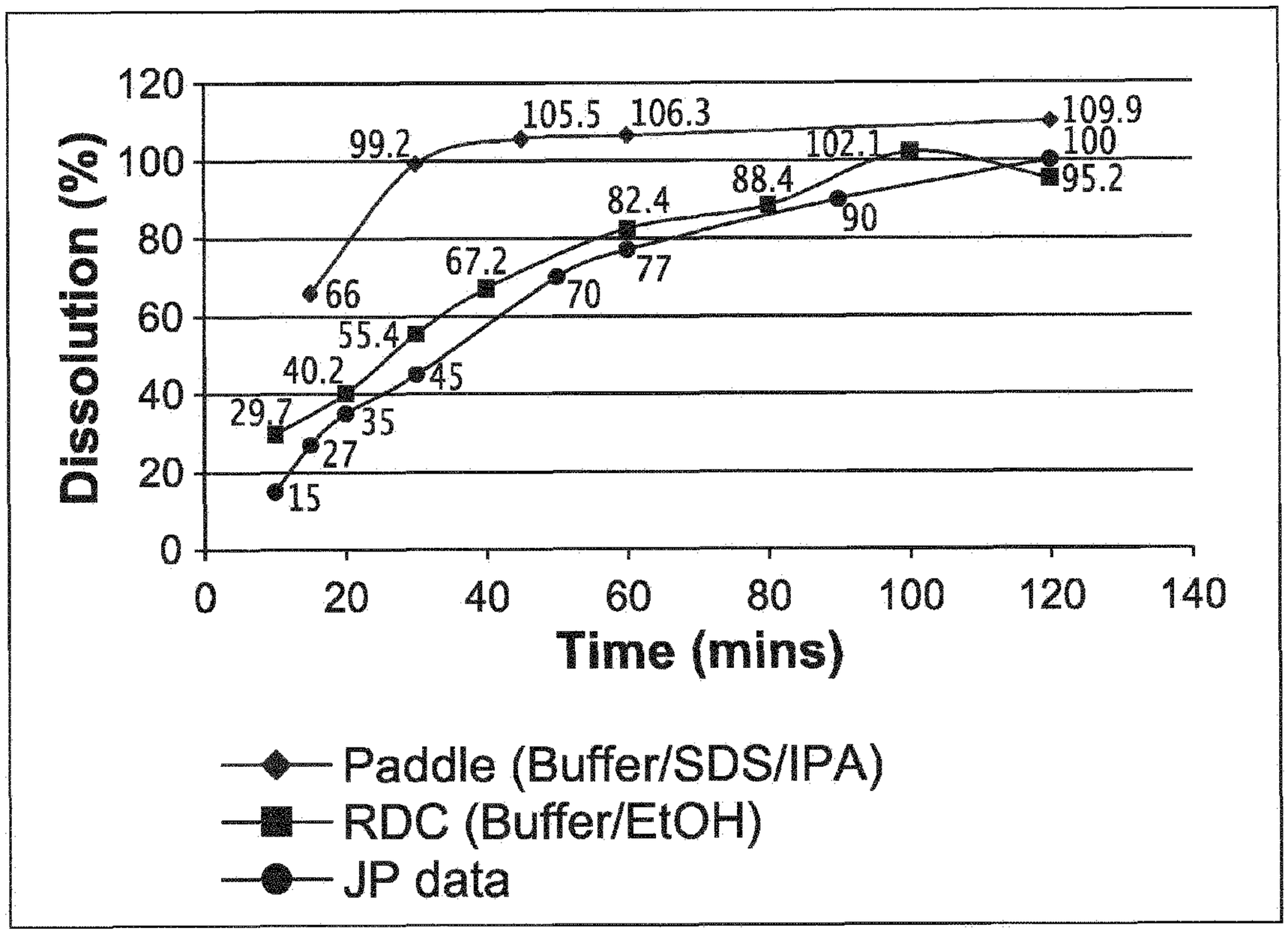
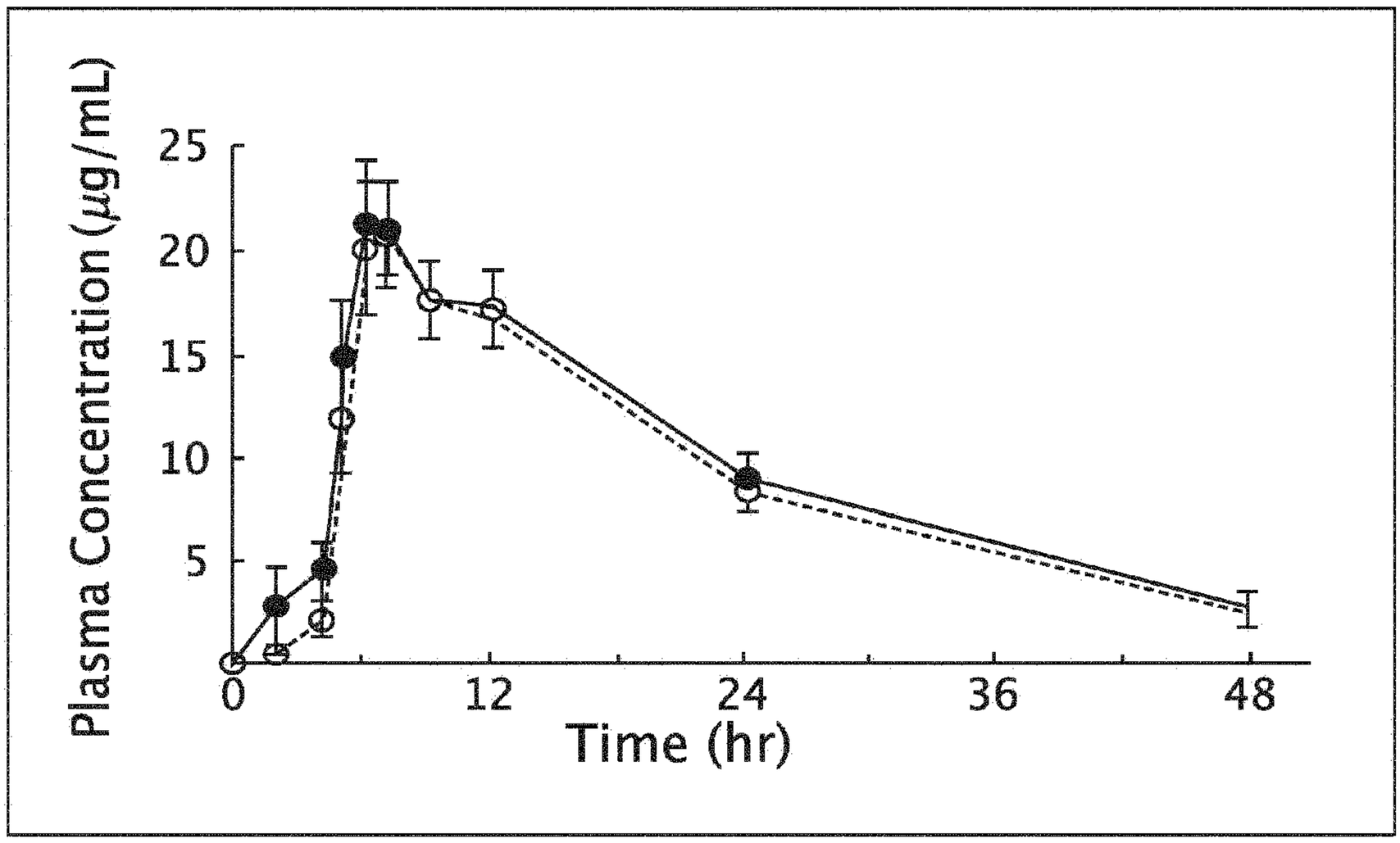


Fig. 1



Plasma Concentrations of EPA after Oral Administration in Humans (n=23, mean±S.E.)

● :Sample I :○ :SampleII

Fig. 2

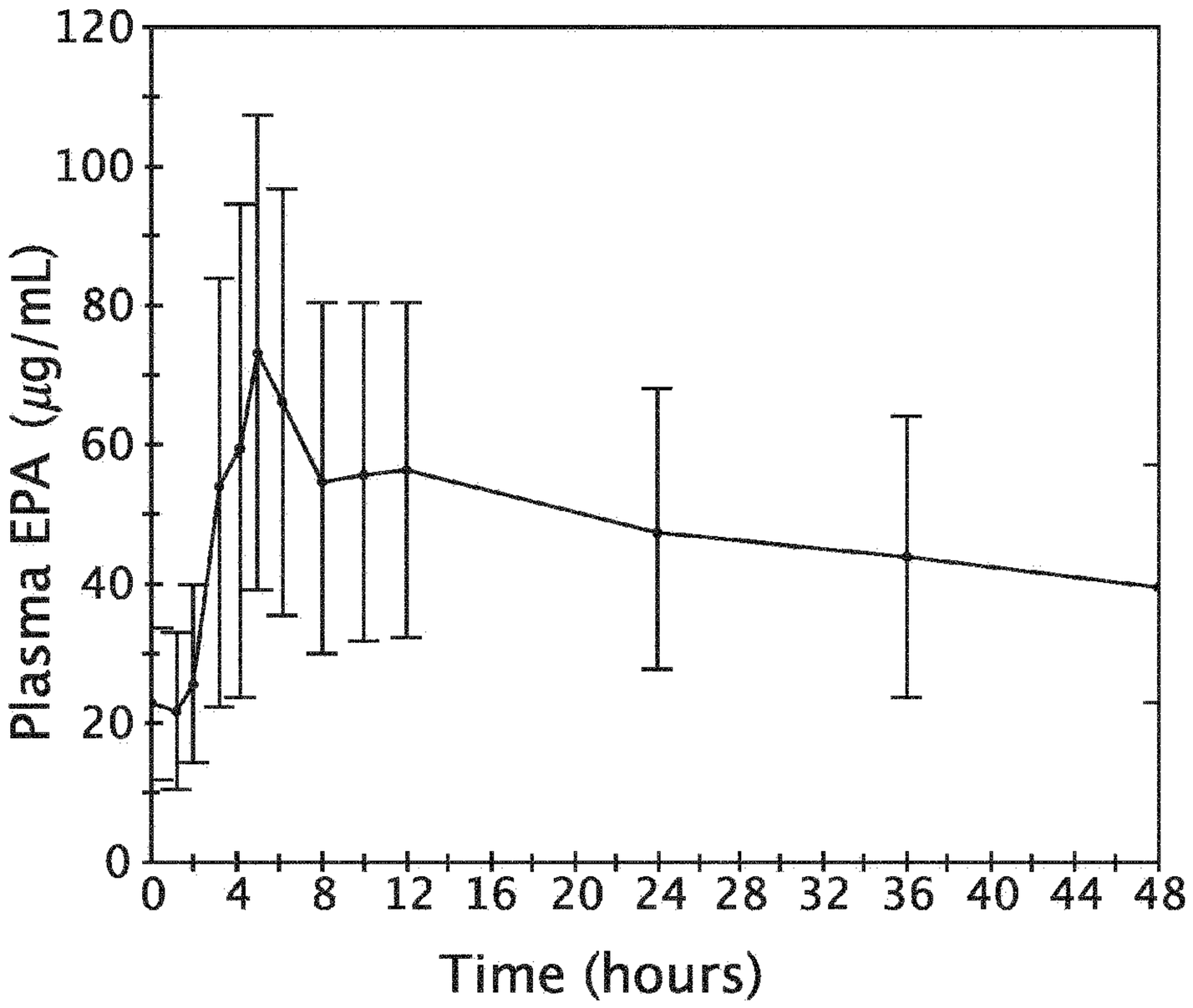

120
100
80
60
40
20
0
Plasma EPA (µg/mL)
0
4
8
12
16
20
24
28
32
36
40
44
48
Time (hours)

Fig. 3