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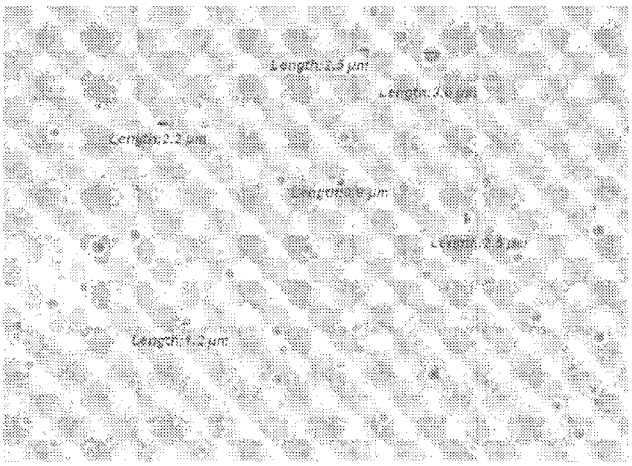
(54) Title: OMEGA-3 FATTY ACID ESTER COMPOSITIONS

FIGURE 1



(57) **Abstract**: Described herein are compositions comprising at least one Omega-3 fatty acid ester and at least one surface active agent; wherein the compositions form micelles when in contact with an aqueous medium. Also provided is a method of administering to a subject a composition comprising at least one Omega-3 fatty acid ester and at least one surface active agent, wherein the at least one Omega-3 fatty acid ester forms micelles when in contact with an aqueous medium, and the bioavailability of the at least one Omega-3 fatty acid ester is substantially independent of a food effect. Said compositions are useful for treating cardiovascular conditions or disorders in a subject and for reducing side effects associated with the ingestion of Omega-3 fatty acid esters. Described are also various dosage forms for administering said compositions and use of said compositions in functional foods. Provided herein are also kits with instructions on how to administer said compositions.

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OMEGA-3 FATTY ACID ESTER COMPOSITIONS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Patent Application No. 61/618,161 filed March 30, 2012.

BACKGROUND

[0002] According to the World Health Organization's (WHO) fact sheet on Cardiovascular Diseases (CVDs), CVDs are the number one cause of death globally. (Fact Sheet No. 317, September 2012 accessed at (http://www.who.int/mediacentre/factsheets/fs317/en/index.html on January 31, 2013). The WHO estimates that an estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to coronary heart disease (CHD) and 6.2 million were due to stroke. The WHO also estimates that by 2030, almost 25 million people will die from CVDs, mainly from heart disease and stroke. The Global Burden of Disease Study estimates that the developing countries contributed 3.5 million of the 6.2 million global deaths from CHD in 1990. (Murray CJL and Lopez AD. The Global Burden of Disease A Comprehensive Assessment of Mortality and Disability from Disease, Injuries and Risk Factors in 1990 and Projected to 2020. Boston, Ma Harvard University Press; 1996). The projections estimate that these countries will account for 7.8 million of the 11.1 million deaths due to CHD in 2020. The developed countries are not immune to CHD. For example, in the USA and Europe, CHD remains the largest single cause of death and disability. In 2005, CHD caused approximately 1 of every 5 deaths in the USA. (Heron MP, et. al. Deaths preliminary data for 2006. Natl. Vital. Stat. Rep. 2008; 56:1-52.) According to the Centers for Disease Control and Prevention it is the leading cause of death in America. Approximately 37% of people who develop a coronary event in a given year will die from it. While major reductions in CVD related mortality have been achieved in Europe, CVD still accounts for 54% of all deaths in women and 43% of all deaths in men.

[0003] CVD is associated with many risk factors. Of these risk factors, hyperlipidemia (e.g., hypertriglyceridemia) and hypercholesterolemia are significant indicators of CVD. As such, dietary supplements, nutraceuticals, and prescribed drugs containing Omega-3 fatty acid esters, such as the ethyl esters of EPA and DHA, are currently used for the treatment of CVD and, in particular, for the reduction of elevated triglycerides.

[0004] However, administration of dietary supplements, nutraceuticals, and prescribed drugs containing Omega-3 fatty acid esters presents significant challenges. For

example, current dietary supplements, nutraceuticals, and prescribed drugs containing Omega-3 fatty acid esters have variable absorption and efficacy when orally administered. In particular, current compositions have a pronounced "food effect," with poor absorption when taken while fasting or with a low fat meal. When taken with fatty foods, the absorption of Omega-3 fatty acid esters improves, due in part to the presence of bile salts that are released in the stomach, which aid absorption of Omega-3 fatty acid esters.

[0005] To overcome low absorption, patients can be dosed with compositions having greater amounts of Omega-3 fatty acid esters, but there are practical limitations to this approach due to the side effects that are commonly associated with such compositions. The oxidative degradation of Omega-3 fatty acid esters that occurs over time can result in an unpleasant aftertaste following administration, especially when consumed in large quantities. Burping and stomach upset are further unpleasant side effects associated with the consumption of Omega-3 fatty acid esters. Following consumption, Omega-3 fatty acid esters tend to float on top of liquid contents in the stomach, forming a layer that prevents the passage of small gas bubbles. When sufficient gas has built up to overcome the surface tension of the oil layer, a person burps. The burps usually contain a fishy taste and smell.

[0006] Accordingly, side effects associated with the administration of current compositions comprising Omega-3 fatty acid esters (e.g., susceptibility to the food effect, large doses to attain efficacy, and the resulting aftertaste, unpleasant smell, and burping) are known to significantly reduce patient compliance.

[0007] While practicing a healthy lifestyle may reduce the incidence of CVD, new therapeutic approaches to manage CVD are warranted. These new approaches might include the discovery of new drugs or improve upon current medications used to treat CVD. The discovery of new drugs, however, comes at a high price with no certainty of eventual success. Accordingly, new or more efficient ways of delivering current medications with a proven safety and efficacy profile should be developed. Thus, there is a need for improved compositions comprising Omega-3 fatty acid esters, such as the ethyl esters of EPA and DHA, that are less susceptible to food effect and which attain high efficacy at lower doses. Ideally, such improved compositions would minimize or eliminate an unpleasant smell and/or an unpleasant aftertaste, and/or burping in the patient. Such an improved composition with reduced side effects would improve patient compliance and more effectively treat the risk factors related to cardiovascular disease.

SUMMARY

[0008] In all of the embodiments provided herein, all of the compositions are free

of Omega-3 free fatty acids. Provided herein, in certain embodiments, are compositions comprising EPA and DHA esters in combination with at least one surface active agent. In certain embodiments, the ratio of EPA ester to DHA ester is from more than 2:1 to not more than 3.4:1. Certain embodiments provide for the ratio of the EPA ester to the DHA ester to be from about 2:1 to about 3.4:1. Provided herein, in certain embodiments, are compositions comprising at least one Omega-3 fatty acid ester and at least one surface active agent. In certain embodiments, the Omega-3 fatty acid ester is selected from the group consisting of hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentenoic acid, docosahexaenoic acid, tetracosapentenoic acid, tetracosahexaenoic acid, or combinations thereof. Certain embodiments provide for compositions comprising the ethyl ester derivative of said Omega-3 fatty acid ester, optionally in combination with at least one surface active agent, at least one terpene, at least one antioxidant, or combinations thereof. Certain embodiments also provide for combinations of different Omega-3 fatty acid esters in ratios of from about 2:1 to about 3.4:1. Other embodiments call for the ratio to be more than 2:1 to not more than 3.4:1. Typically, the ratio is about 2.4:1. Certain embodiments provide a method for treating a variety of conditions or disorders that can be treated by administering said Omega-3 fatty acid esters in compositions described herein comprising the described ratios, optionally with at least one surface active agent, at least one terpene, at least one antioxidant, or combinations thereof. The compositions described herein minimize several side effects found in currently marketed compositions containing Omega-3 fatty acid esters that can deter a human subject from complying with dosing regimen necessary to treat a condition or disorder treatable by administration of Omega-3 fatty acid esters. In certain embodiments, the bioavailability of said Omega-3 fatty acid esters when administered as certain compositions described herein is substantially the same when administered with or without food, i.e., substantially independent of food effect, to a human subject in need of such administration.

[0009] Thus, certain embodiments call for pharmaceutical compositions comprising at least one Omega-3 fatty acid ester and at least one surface active agent; wherein said at least one Omega-3 fatty acid ester comprises at least about 40% (wt/wt) of the composition.

[0010] Certain embodiments call for pharmaceutical compositions comprising a first Omega-3 fatty acid ester selected from the group consisting of hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentenoic acid, docosahexaenoic acid, tetracosapentenoic acid, tetracosahexaenoic acid, and a second Omega-3 fatty acid ester

selected from the group consisting of hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentenoic acid, docosahexaenoic acid, tetracosapentenoic acid, tetracosahexaenoic, such that the first and second Omega-3 fatty acid esters selected are different from each other and the ratio of the first and second Omega-3 fatty acid esters are in a ratio of more than 2:1 to not more than 3.4:1 (first Omega-3 fatty acid ester:second Omega-3 fatty acid ester); wherein the first and second Omega-3 fatty acid esters combined comprise at least about 40% (wt/wt) of the composition and wherein said composition is substantially free of active ingredients other than said Omega-3 fatty acid esters.

[0011] Certain embodiments call for the use of at least one Omega-3 fatty acid ester. Typically, the Omega-3 fatty acid ester is an ethyl ester.

[0012] Certain embodiments call for pharmaceutical compositions comprising at least one Omega-3 fatty acid ester and at least one terpene; wherein said at least one Omega-3 fatty acid ester comprises at least about 40% (wt/wt) of the composition and is substantially free of active ingredients other than Omega-3 fatty acid esters. In certain embodiments, the at least one Omega-3 fatty acid ester comprises about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, The terpene is typically, but not necessarily d-limonene. In certain other embodiments, such compositions comprise natural orange-oil.

[0013] Certain embodiments provide for compositions comprising EPA ethyl esters and DHA ethyl esters and at least one terpene, wherein the ratio of EPA:DHA is about 2.4:1 and wherein said EPA and DHA ethyl esters combined comprise from about 40% (wt/wt) to about 95% (wt/wt) of said composition. In certain embodiments, the EPA and DHA ethyl esters combined comprise about 40% (wt/wt) of said composition. The terpene is typically, but not necessarily d-limonene. In certain other embodiments, such compositions comprise natural orange-oil.

[0014] In embodiments comprising substantially pure d-limonene, the d-limonene is from about 95% to about 98% pure. In certain embodiments, the substantially pure d-limonene is at least 95%, 96%, 97% or 98% pure.

[0015] In certain embodiments, the Omega-3 fatty acid ester is selected from the group consisting of at least one EPA ester, at least one DHA ester or combinations thereof, and comprises at least one surface active agent. In certain embodiments, the at least one EPA ester and at least one DHA ester is substantially pure. Certain embodiments also provide for compositions comprising at least one EPA ester and at least one DHA ester in ratios from about 2:1 to about 3.4:1, which are substantially free of active ingredients other than Omega-3 fatty acid esters. Compositions comprising other ratios are also described. Certain compositions can also be free of natural orange oil

or d-limonene. In certain embodiments, the Omega-3 fatty acid esters comprise at least 40% of the composition. Typically, the Omega-3 EPA and DHA esters are ethyl esters. Certain compositions described herein form micelles in an aqueous medium and are free of food effect. Certain compositions, when administered with or without food, are substantially free of food effect. Provided herein are also methods for treating cardiovascular conditions or disorders using the compositions described. The compositions described herein minimize or eliminate side effects when compared to the administration of prior art compositions. Also provided are packaged compositions or kits of the Omega-3 fatty acid esters comprising one or more unit dosage forms together with instructions on using the compositions.

[0016] Accordingly, in at least one embodiment is provided, a pharmaceutical composition comprising at least one EPA ester and at least one DHA ester in a weight to weight ratio of more than about 2:1 to not more than about 3.4:1 (EPA:DHA) and at least one surface active agent, wherein said EPA and DHA esters combined comprises from about 40% to about 85% by weight of the composition. In certain such embodiments, the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

[0017] In at least one other embodiment is provided, a pharmaceutical composition comprising at least one EPA ester and at least one DHA ester in a weight to weight ratio from about 2:1 to about 3.4:1 (EPA:DHA) and at least one surface active agent, wherein said EPA and DHA esters combined comprises from about 40% to about 85% by weight of the composition. In certain such embodiments, the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

[0018] In at least one other embodiment is provided, a pharmaceutical composition comprising at least one EPA ester and at least one DHA ester in a weight to weight ratio of more than 2:1 to not more than 3.4:1 (EPA:DHA) and at least one surface active agent, wherein said EPA and DHA esters combined comprises from about 40% to about 85% by weight of the composition. In certain such embodiments, the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

[0019] In at least one other embodiment is provided, a pharmaceutical composition comprising at least one EPA ester and at least one DHA ester in a weight to weight ratio of more than 2:1 to not more than 3.4:1 (EPA:DHA) and at least one surface active agent, wherein said EPA and DHA esters combined comprises from about 40% to about 85% by weight of the composition, and wherein the composition when administered with or without food to a human subject in need of such administration is substantially independent of food effect. In certain such embodiments, the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

[0020] In at least one embodiment, the compositions described herein comprise

substantially pure at least one EPA ester and/or at least one DHA ester.

[0021] In at least one embodiment, the compositions described herein consist essentially of the at least one EPA ester and/or the at least one DHA ester.

[0022] In certain embodiments, either of, or each of, the EPA and DHA ester comprising the composition is the ethyl ester.

[0023] In certain embodiments, the compositions described herein comprise substantially pure EPA ethyl ester and/or substantially pure DHA ethyl ester.

[0024] In certain embodiments, the compositions described herein consist essentially of substantially pure EPA ethyl ester and/or substantially pure DHA ethyl ester.

[0025] In certain embodiments, the ratio of the EPA and DHA ester comprising the composition is about 2.4:1 (EPA ester:DHA ester).

[0026] Certain embodiments call for compositions comprising either natural orange oil from about 0.1% to about 5% (wt/wt) of said composition. In embodiments comprising natural orange oil the natural orange oil is present at about 1.6% (wt/wt) of the composition. Certain other embodiments comprise substantially pure d-limonene from about 0.1% to about 5%. In embodiments comprising substantially pure d-limonene, the d-limonene is present at about 1.5% (wt/wt) of the composition.

[0027] In certain embodiments, the pharmacologic effect of the compositions described herein is substantially independent of a food effect upon administration to a subject.

[0028] In at least one embodiment, a pharmaceutical mixed-fatty-acids composition in which, a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acids (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acids (DHA) in a weight ratio of EPA:DHA of from about 1:2 to about 2:1; b) (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid is present in an amount of at least one percent by weight; and c) at least one surface active agent is provided. These compositions can optionally further comprise natural orange oil from about 0.1% to about 5% (wt/wt) or substantially pure d-limonene from about 0.1% to about 5% (wt/wt) of the composition. The natural orange oil is typically present at about 1.6% (wt/wt) of said composition and d-limonene is typically present at about 1.5% (wt/wt) of the composition.

[0029] In at least one embodiment, a mixed-fatty-acids composition for the treatment or prophylaxis of at least one of the multiple risk factors for CVD in which, a) at least 80% by weight of the composition is comprised of Omega-3 fatty acids; b) at least 80% by weight of the total fatty acid content of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z

omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, c) Omega-3 fatty acids other than EPA and DHA are present in an amount of at least 1.5% by weight of the total fatty acids; and c) at least one surface active agent is provided. These compositions can optionally further comprise natural orange oil from about 0.1% to about 5% (wt/wt) or substantially pure d-limonene from about 0.1% to about 5% (wt/wt) of the composition. The natural orange oil is typically present at about 1.6% (wt/wt) of said composition and d-limonene is typically present at about 1.5% (wt/wt) of the composition.

[0030] In at least one embodiment a pharmaceutical mixed-fatty-acids composition in which, a) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:2 to 2:1, b) at least 3% by weight of the composition is comprised of Omega-3 fatty acids other than EPA and DHA that have 18, 20, 21, or 22 carbon atoms, and c) at least one surface active agent is provided. These compositions can optionally further comprise natural orange oil from about 0.1% to about 5% (wt/wt) or substantially pure d-limonene from about 0.1% to about 5% (wt/wt) of the composition. The natural orange oil is typically present at about 1.6% (wt/wt) of said composition and d-limonene is typically present at about 1.5% (wt/wt) of the composition.

[0031] In at least one embodiment, a pharmaceutical mixed-fatty-acids composition in which, a) at least 90% by weight of the composition is comprised of long chain, polyunsaturated, Omega-3 fatty acids; b) at least 80% by weight of the composition is comprised of a combination of (all-Z omega-3)-5,8,11,14,17-eicosapentaenoic acid (EPA) and (all-Z omega-3)-4,7,10,13,16,19-docosahexaenoic acid (DHA) in a weight ratio of EPA:DHA of from 1:1 to 2:1, with the EPA constituting 40 to 60% by weight of the composition and the DHA constituting 25 to 45% by weight of the composition; c) at least 4.5% by weight of the composition is comprised of Omega-3 fatty acids other than EPA and DHA that have 18, 20, 21, or 22 carbon atoms; d) from 1 to 4% by weight of the composition is comprised of (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid; e) at least one surface active agent; and f) the composition is in oral dosage form and includes an effective amount of a pharmaceutically acceptable antioxidant. These compositions can optionally further comprise natural orange oil from about 0.1% to about 5% (wt/wt) or substantially pure d-limonene from about 0.1% to about 5% (wt/wt) of the composition. The natural orange oil is typically present at about 1.6% (wt/wt) of said composition and d-limonene is typically present at about 1.5% (wt/wt) of the composition.

[0032] It should be noted that in all of the embodiments comprising

compositions described herein, the total of all ingredients comprising the composition does not exceed 100%.

[0033] In certain embodiments is provided, a pharmaceutical or drug composition comprising EPA and DHA in a weight to weight ratio of about 3.5:1 to about 5:1 and at least one surface active agent, and wherein the composition is more than 84% combined EPA and DHA by weight. These compositions can optionally further comprise natural orange oil from about 0.1% to about 5% (wt/wt) or substantially pure d-limonene from about 0.1% to about 5% (wt/wt) of the composition. The natural orange oil is typically present at about 1.6% (wt/wt) of said composition and d-limonene is typically present at about 1.5% (wt/wt) of the composition.

[0034] Certain embodiments provide for certain compositions comprising at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA), at least one surface active agent, substantially no docosahexaenoic acid (DHA) or its esters. These compositions can optionally further comprise natural orange oil from about 0.1% to about 5% (wt/wt) or substantially pure d-limonene from about 0.1% to about 5% (wt/wt) of the composition. The natural orange oil is typically present at about 1.6% (wt/wt) of said composition and d-limonene is typically present at about 1.5% (wt/wt) of the composition.

[0035] In at least one embodiment, a method is provided for treating the following disorders: metabolic syndrome, macular degeneration, Omega-3 deficiency, cognitive impairment, including as a result of surgery or traumatic brain injury (such as, for example, resulting from a concussion), major depression, suicide, post-partum depression, inflammation, primary sclerosing cholangitis, borderline personality disorder in women, breast cancer, non-alcoholic fatty acid liver disease, and improvement in cognition and behavior in children. These conditions or disorders can be treated by administering the compositions described herein to a subject, typically a human, in need of such administration.

[0036] In at least one embodiment, a method is provided for treating at least one cardiovascular condition or disorder in a subject in need of such treatment, said method comprising administering to a subject at least one composition described herein comprising a therapeutically effective amount of the Omega-3 fatty acid esters and at least one surface active agent.

[0037] In at least one embodiment a method is provided for treating at least one cardiovascular condition or disorder, for example and without limitation disorders of the heart and vasculature, including, for example, hypertension, hyperlipidemia, hypertriglyceridemia, atherosclerosis, transient ischemic attack, systolic dysfunction, diastolic dysfunction, aneurysm, aortic dissection, myocardial ischemia, acute myocardial infarction (AMI), acute ST-segment elevation myocardial infarction (STEMI), acute non-

ST -segment elevation myocardial infarction (NSTEMI), angina pectoris, unstable angina (UA), and stable angina (SA), myocardial infarction, congestive heart failure, dilated congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, corpulmonale, arrhythmia, valvular heart disease, endocarditis, pulmonary embolism, venous thrombosis, peripheral vascular disease, and peripheral artery disease. The method comprises administering to a subject in need of treatment a therapeutically effective amount of a composition described herein.

[0038] In at least one embodiment, a method is provided for treating hypertension and/or hyperlipidemia.

[0039] In at least one other embodiment, a method is provided for treating hypertriglyceridemia.

[0040] In certain embodiments, the total amount of triglycerides (TG) in a human subject's blood having ≥ 150 mg TG per dL of serum at the start of the dosing regimen is reduced by at least 20% within about 30 days following administration of certain embodiments of the compositions described herein.

[0041] In at least one other embodiment, a method is provided for treating a human subject having ≥ 150 mg TG per dL of serum who is in need of such treatment, said method comprising administering to the human subject at least one embodiment of the composition described herein comprising a therapeutically effective amount of Omega-3 fatty acid esters.

[0042] Embodiments are also provided wherein the compositions described herein are packaged together as a kit with instructions on how to use the compositions for treating cardiovascular conditions or disorders.

[0043] In certain embodiments, the surface active agent is selected from the group consisting of at least one nonionic surface active agents, cationic surface active agents, anionic surface active agents, zwitterionic surface active agents, or combinations thereof

[0044] In certain embodiments, the surface active agent is selected from the group consisting of at least one anionic surface active agent, at least one non-ionic surface active agent, and a combination thereof.

[0045] In certain embodiments comprising at least one surface active agent, the at least one surface active agent has a hydrophilic-lipophilic balance (HLB) of about 8.0.

[0046] In certain embodiments comprising at least one surface active agent, the surface active agent can be a non-ionic surface active agent selected from the group consisting of at least one polysorbate, at least one poloxamer, and a combination thereof.

[0047] In certain embodiments, the at least one surface active agent comprises a polysorbate present from about 15% wt/wt to about 31% wt/wt of the composition. In

certain embodiments, the polysorbate is polysorbate 80.

[0048] In certain other embodiments, the at least one surface active agent comprises a poloxamer present from about 0.1% to about 5% wt/wt of the composition.

[0049] In certain embodiments, the compositions described herein comprise a combination of polysorbate 80 and the poloxamer Pluronic F87 $[(HO(C_2H_4O)_{64}(C_3H_6O)_{37}(C_2H_4O)_{64}H]$.

[0050] In certain embodiments, the composition further comprises at least one antioxidant. In such embodiments the at least one antioxidant is selected from the group consisting of a tocopherol, a tocotrienol, or combinations thereof. In such embodiments, the tocopherol, tocotrienol or combinations thereof is present from about 0.01% to about 5% by weight of the compositions. In certain such embodiments, the tocopherols, tocotrienols or combinations thereof can be present at about 0.01%, 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5% by weight of the compositions. In certain such embodiments, the tocopherols, tocotrienols, or combinations thereof can be present at about 0.4% by weight of the compositions. In certain embodiments, the tocopherol, tocotrienol or combinations is present at about 0.4% by weight of the composition. In certain embodiments further comprising at least one antioxidant, the antioxidant is a tocopherol at about 0.4% by weight of the composition.

[0051] In certain embodiments, the composition self-micellizes in an aqueous medium. In certain other embodiments, the aqueous medium is water. In certain other embodiments, the aqueous medium has an acidic pH. In certain other embodiments, the aqueous medium is 0.1N HCl.

[0052] In certain embodiments, the compositions described herein self-micellizes in an aqueous medium wherein the micelles have a diameter from about 1 μm to about 10 μm. In certain embodiments, the compositions described herein self-micellizes in an aqueous medium having an acidic pH, wherein the micelles have a diameter from about 1 μm to about 10 μm. In certain other embodiments, the compositions described herein self-micellizes in 0.1N HCL, wherein the micelles have a diameter from about 1 μm to about 10 μm. In certain embodiments, the micelles have an average diameter of about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 μm.

[0053] In certain embodiments, the compositions described herein can be administered with or without food to a human subject in need of such administration wherein the bioavailability of the Omega-3 fatty acid esters comprising the compositions are substantially independent of food effect.

[0054] Certain embodiments provide for compositions that minimize or eliminate at least one side effect from the administration of a composition of the present disclosure

when compared to the administration of a composition comprising Omega-3 fatty acid esters substantially free of a surface active agent. In other embodiments, non-limiting examples of the side effects include regurgitation, frequency of burping, gastroesophageal reflux disease (GERD), bloating, increased intestinal gas, fish taste, fishy breath, fish smell, nausea, diarrhea, or combinations thereof.

[0055] In certain embodiments, the compositions described herein comprise d-limonene or natural orange oil. Such compositions can minimize or eliminate at least one side effect from the administration of a composition of the present disclosure when compared to the administration of a composition comprising Omega-3 fatty acid esters substantially free of d-limonene or natural orange oil. In other embodiments, non-limiting examples of the side effects include regurgitation, frequency of burping, gastroesophageal reflux disease (GERD), bloating, increased intestinal gas, fish taste, fishy breath, fish smell, nausea, diarrhea, or combinations thereof.

[0056] In certain embodiments, the compositions described herein when administered to a human subject selected from the group consisting of individuals having from about 155 to about 199 mg TG per dL of serum, from about 200 to about 499 mg TG per dL of serum and from about 500 mg or higher TG per dL of serum, lowers said subject's serum TG levels by at least about 20%.

[0057] Certain embodiments of the compositions described herein can be administered to a human subject in need of such administration with a non-Omega-3 fatty acid ester lipid-lowering agent selected from the group consisting of cholesterol absorption inhibitors, bile acid sequestrants/resins, statins, niacin and derivatives, MTP inhibitors, fibrates and CETP inhibitors.

[0058] In certain embodiments, the compositions described herein can reduce the total amount of TG in the serum of a human subject being treated for hypertriglyceridemia by at least about 20% within about 30 days of administration of the composition wherein the human subject's blood measures ≥ 150 mg TG per dL of serum at the start of the dosing regimen.

[0059] In at least one embodiment, the compositions described herein can be administered orally or parenterally in a suitable dosage form. When administered orally, the compositions described herein can be administered, typically, but not necessarily, in the form of a gel or liquid capsule.

[0060] In certain other embodiments, methods are provided for administering at least about 0.5g/day of certain embodiments of the compositions described herein comprising from about 40% to about 85% by weight of the composition, at least one EPA ester and at least one DHA ester in a ratio of more than 2:1 to not more than 3.4:1 and at least one surface active agent. Typically, but not necessarily, the ester is an ethyl ester

and the at least one surface active agent is polysorbate 80, Pluronic F87 or a combination thereof. In certain such embodiments, the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition. Optionally, the composition can further comprise substantially pure d-limonene or natural orange oil.

[0061] In certain other embodiments, methods are provided for administering at least about 4g/day of certain embodiments of the compositions described herein comprising ethyl eicosapentaenoic acid (ethyl-EPA), at least one surface active agent and substantially no docosahexaenoic acid (DHA), where the ethyl-EPA constitutes at least about 96% by weight of the total Omega-3 fatty acid esters in the composition. In certain embodiments, such compositions can further comprise natural orange oil or substantially pure d-limonene.

[0062] Certain embodiments provide for the use of the compositions described herein in the manufacture of a medicament for the treatment of a cardiovascular disease or disorder. In certain embodiments, the cardiovascular disease or disorder is hyperlipidemia. In certain other embodiments, the cardiovascular disease or disorder is hypercholesterolemia. In certain embodiments, the cardiovascular disease or disorder is hypertriglyceridemia.

[0063] Certain embodiments provide for the use of the compositions described herein in the manufacture of a medicament for the treatment of a cardiovascular disease or disorder. In certain embodiments, the cardiovascular disease or disorder is hyperlipidemia. In certain other embodiments, the cardiovascular disease or disorder is hypercholesterolemia. In certain embodiments, the cardiovascular disease or disorder is hypertriglyceridemia.

[0064] In certain embodiments, administration of the compositions described herein provide for a blood serum concentration in a human subject of at least about 20 nmol/mL of combined at least one EPA ester and at least one DHA ester within about four hours after administration of the certain embodiments.

[0065] Also provided are kits comprising compositions of the Omega-3 fatty acid esters as one or more unit dosage forms together with instructions on using the dosage forms. In certain embodiments, the dosage forms described herein can be packaged as blister packs or in bottles with instructions for using the dosage forms. For example, the instructions can be provided as a package insert or directly on a label attached to the blister pack, bottle or on secondary packaging in which the blister pack or bottle was provided to a human subject. The instructions can include, for example, dosing frequency, administration of the dosage forms with or without food, the active ingredients comprising the dosage forms, and the cardiovascular conditions or disorders that would benefit from administration of the dosage forms.

[0066] In certain embodiments kits are provided, wherein certain dosage forms comprising the compositions described herein can be packaged together with other non-Omega-3 fatty acid ester lipid lowering agents. The kit(s) comprise one or more unit dosage forms of certain embodiments of the compositions described herein together with one or more unit dosage forms comprising the non-Omega-3 fatty acid ester lipid-lowering agents together with instructions on using the dosage forms.

[0067] Certain embodiments provide for a functional food(s) for treating and/or preventing CVD comprising the compositions described herein.

[0068] Certain embodiments provide methods of treating CVD by administering a functional food comprising the compositions described herein.

[0069] Certain embodiments provide for a functional food(s) comprising the compositions described herein, and methods to treat hypertriglyceridemia in a human subject.

BRIEF DESCRIPTION OF THE DRAWING

[0070] *Figure 1* depicts a photomicrograph of an embodiment. A composition comprising micelles, as described herein, was prepared, added between a slide and cover slip, observed at 40X magnification with a Nikon Model Trinocular Head and a Spot RT3 digital camera, and the diameters of several representative micelles were measured.

[0071] *Figure 2* shows a schematic flowchart of the process for manufacturing one embodiment of the compositions described herein.

[0072] *Figure 3* shows a schematic flowchart of the process for manufacturing the gel mass for encapsulating one embodiment of the compositions described herein.

[0073] *Figure 4* shows the a schematic flowchart of the encapsulation process for manufacturing one dosage form comprising one embodiment of the compositions described herein.

DETAILED DESCRIPTION

[0074] Certain aspects, modes, embodiments, variations and features of the invention are described herein in various levels of detail to provide further understanding of embodiments related to compositions comprising Omega-3 fatty acid esters, and methods related to using such compositions containing a high concentration of Omega-3 fatty acid esters. In certain embodiments, an EPA ester and DHA ester are present in specific weight ratio percentages and relative amounts. As noted, these compositions have beneficial effects on certain risk factors for CVD, including the lowering of serum triglycerides and serum cholesterol.

DEFINITIONS

[0075] As used herein, the term "composition(s)" or "formulation(s)" includes therapeutic and dietary compositions including, but not limited to a dietary supplement, nutraceutical formulation, or pharmaceutical formulation. Further, the terms composition, dietary supplement, nutraceutical formulation, and pharmaceutical formulation are used interchangeably herein.

[0076] As used herein, the term "EPA" refers inclusively to (5Z,8Z,11Z,14Z,17Z)-eicosa- 5,8,11,14,17-pentenoic acid or derivatives thereof, including alkyl esters, such as, for example, the ethyl ester.

[0077] As used herein, the term "DHA" inclusively refers to (4Z,7Z,10Z,13Z,16Z,19Z)- docosa-4,7,10,13,16,19-hexaenoic acid or derivatives thereof, including alkyl esters, such as, for example, the ethyl ester.

[0078] As used herein, the term "micelle" (plural micelles, micella, or micellae) refers to an aggregate of molecules, that have assembled into an approximately spherical core/shell architecture, and are suspended in an aqueous phase. A typical micelle in aqueous solution forms an aggregate with the hydrophilic "head" regions in contact with surrounding solvent and/or in contact with the polar region of one or more surface active agent(s), sequestering the hydrophobic regions in the micelle center. Micelles are approximately spherical in shape.

[0079] The term "self-micellizes" as used herein refers to the process in which micelles are formed in an aqueous medium without the introduction of energy, including agitation or shearing.

[0080] As used herein, the term "aqueous medium" refers to any solution or suspension, that comprises water, including for example, without limitation, water by itself; phosphate buffered saline pH 7.4, Sprite, apple juice, G-2 fruit punch, and chocolate milk. In certain embodiments, an aqueous medium comprises at least one fluid having an acidic pH. In certain other embodiments, an aqueous medium comprises a biological fluid such as, for example and without limitation, stomach acid. In other embodiments, the aqueous medium comprises simulated stomach acid comprising 0.1N HCl.

[0081] As used herein, the term "free fatty acid" refers to one or more polyunsaturated fatty acids that have not been modified or do not have any other groups attached.

[0082] As used herein, the term "ester" refers to the replacement of the hydrogen in the carboxylic acid group of a polyunsaturated fatty acid molecule with another substituent. Typical esters are known to those in the art, a discussion of which is provided by Higuchi, T. et al., *Pro-drugs as Novel Delivery Systems*, Vol. 14, A.C.S. Symposium

Series, *Bioreversible Carriers in Drug Design*, Ed. Edward B. Roche, Amer. Pharma. Assoc., Pergamon Press (1987), and *Protective Groups in Organic Chemistry*, McOmie ed., Plenum Press, New York (1973), each of which is incorporated herein by reference in the entirety. Examples of common esters include methyl, ethyl, trichloroethyl, propyl, butyl, pentyl, tert-butyl, benzyl, nitrobenzyl, methoxybenzyl, benzhydryl, monoglyceride, diglyceride, triglyceride.

[0083] As used herein, the term "monoglyceride" refers to a fatty acid chain, such as DHA or EPA molecule, covalently bonded to a glycerol molecule through an ester linkage. As used herein, the term "diglyceride" refers to a fatty acid chain such as DHA or EPA, covalently bonded to a glycerol molecule through an ester linkage, wherein the glycerol molecule is further bonded to one additional fatty acid chain, which may or may not be DHA or EPA, through one additional ester linkage. As used herein, the term "triglyceride" refers to a fatty acid chain, such as DHA or EPA, covalently bonded to a glycerol molecule through an ester linkage, wherein the glycerol molecule is further bonded to two additional fatty acid chains, either or both of which may or may not be DHA or EPA, through two additional ester linkages.

[0084] As used herein, the term "terpene" refers to the large and diverse class of organic compounds produced by a variety of plants, particularly conifers. When terpenes are modified chemically, such as by oxidation or rearrangement of the carbon skeleton, the resulting compounds are generally referred to as "terpenoids" (e.g., carvone). Terpenes and terpenoids are the primary constituents of the essential oils of many types of plants and flowers.

[0085] As used herein, the terms "α-Tocopherol," "tocopherol," and "vitamin E" each refer to a set of tocopherols and tocotrienols, which are fat-soluble vitamins with antioxidant properties.

[0086] As used herein, the term "antioxidant" refers to a molecule capable of inhibiting the oxidation of other molecules. Oxidation is a chemical reaction that transfers electrons or hydrogen from a substance to an oxidizing agent. Oxidation reactions can produce free radicals. In turn, these radicals can start chain reactions. When the chain reaction occurs in a cell, it can cause damage or death to the cell. Antioxidants terminate these chain reactions by removing free radical intermediates, and inhibit other oxidation reactions. They do this by being oxidized themselves, so antioxidants are often reducing agents such as thiols, ascorbic acid, or polyphenols. Exemplary antioxidants include rosemary oil, ascorbic acid (vitamin C), glutathione, lipoic acid, uric acid, carotenes, melatonin, ubiquinol (coenzyme Q), α-tocopherol (vitamin E), acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, and potassium metabisulfite.

[0087] As used herein, a pharmaceutically acceptable "carrier" refers to any substance suitable as a vehicle for delivering a molecule or composition to a suitable in vivo site of absorption. Examples of such carriers include, but are not limited to water, phosphate buffered saline (PBS), Ringer's solution, dextrose solution, serum-containing solutions, Hank's solution and other aqueous physiologically-balanced solutions.

[0088] As used herein, a pharmaceutically acceptable "preservative" includes but is not limited to potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol,phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

[0089] As used herein, a "coloring agent" provides coloration to the composition or dosage form. Such coloring agents include food grade dyes.

[0090] As used herein, the term "subject" refers to a mammal, including but not limited to a dog, cat, horse, cow, pig, sheep, goat, chicken, rodent, primate or human. Subjects include animals such as house pets (e.g., dogs, cats, and the like), agricultural stock subjects (e.g., cows, horses, pigs, chickens, etc.), laboratory subjects (e.g., mice, rats, rabbits, etc.), but are not so limited. The human subject may be a pediatric, adult, or a geriatric subject. The human subject may be of either gender.

[0091] As used herein, the terms "cardiovascular disease" and "cardiovascular condition" include disorders of the heart and vasculature, including, for example, hypertension, hyperlipidemia, hypertriglyceridemia, atherosclerosis, transient ischemic attack, systolic dysfunction, diastolic dysfunction, aneurysm, aortic dissection, myocardial ischemia, acute myocardial infarction (AMI), acute ST-segment elevation myocardial infarction (STEMI), acute non-ST -segment elevation myocardial infarction (NSTEMI), angina pectoris, unstable angina (UA), and stable angina (SA), myocardial infarction, congestive heart failure, dilated congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, corpulmonale, arrhythmia, valvular heart disease, endocarditis, pulmonary embolism, venous thrombosis, peripheral vascular disease, and peripheral artery disease.

[0092] Hypertriglyceridemia, for example, is a condition related to cardiovascular disease in which fasting blood serum concentrations of triglycerides are ≥ 150 mg/dL. Blood concentrations can rise from moderately high levels of 200 mg/dL to 500 mg/dL, or in severe cases, above 500 mg/dL. The American Heart Association has categorized triglyceride concentrations as "normal" (below 150 mg/dL), "elevated" (150 to 199 mg/dL), "high" (200 to 499 mg/dL), and "very high" (above 500 mg/dL). It will be evident to the skilled practitioner that the categorization of hypertriglyceridemia can vary from country to country. For example, Canadian and European guidelines recommend

fasting blood serum triglyceride levels of less than 1.7 mmol/L as “desirable”, from 1.7 to 2.2 mmol/L as “borderline high” and 2.3 to 5.6 mmol/L as “high” and above 5.6 mmol/L as “very high”. The skilled practitioner will also appreciate that what constitutes elevated blood serum triglyceride levels may vary based on age and gender.

[0093] As used herein, an "effective amount" or "therapeutically effective amount" of a composition as described in some embodiments herein can be a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, for example, an amount which results in the prevention of, or a decrease in the symptoms associated with, a disease that is being treated. The amount of composition administered to the subject, particularly one in need of the composition, can depend on the type and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. A person skilled in the art will be able to determine appropriate dosages depending on these and other factors. Typically, an effective amount of the compositions described herein can be sufficient for achieving a therapeutic or prophylactic effect.

[0094] The terms "dose unit," "unit dose," and "dosage unit," as used herein, refer to a portion of a composition that contains an effective amount of an active suitable for a single administration to provide, or contribute to, a therapeutic effect. Such dosage units may be administered one to a plurality (i.e., 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

[0095] The term "food effect," as used herein, refers to a relative difference in AUC (area under the curve), C_{max} (maximum plasma concentration), and/or T_{max} (time to maximum concentration) of an active substance, when said substance or a composition thereof, such as a tablet, a capsule or a liquid, is administered orally to a subject concomitantly with food or in a fed state as compared to the same values when the same composition is administered in a fasted state. The food effect, F, is calculated as:

$$F=(Y_{fed}-Y_{fasted})/Y_{fasted}$$

wherein Y_{fed} and Y_{fasted} are the found values of AUC, C_{max}, or T_{max} in the fed and fasted state, respectively. A food effect, F, is generally established when $F > 1$.

[0096] In general, the term “AUC” or “area under the plasma concentration-time curve” is related to the total amount of an active measurable in the systemic circulation following administration of a single dose. The AUC is a mathematical and visual representation of the aggregate amount of the active in the systemic circulation over a given period of time. Changes in the AUC need not necessarily reflect changes in the total amount of the active absorbed but can reflect modifications in the kinetics of

distribution, metabolism and excretion. Accordingly, the term AUC as used herein refers to the total amount of Omega-3 fatty acids measurable in the systemic circulation following administration of a single dose of any of the compositions described herein.

[0097] The term "T_{max}" or "time of peak concentration" refers to the period of time required to achieve peak plasma concentration of an active after administration of a single dose. Accordingly, the term T_{max} as used herein refers to the period of time required to achieve peak plasma concentration of Omega-3 fatty acid esters after administration of a single dose of any of the compositions described herein.

[0098] The term "C_{max}" or "peak concentration" is the highest concentration of an active achieved in the blood plasma. Accordingly, the term C_{max} as used herein refers to the maximum concentration of Omega-3 fatty acid esters after administration of a single dose of any of the compositions described herein.

[0100] The term "substantially independent of a food effect," or "substantially free of food effect" as used herein, refers to a substantial elimination of the effect of food upon the absorption (e.g., F is about 0), following oral administration, of any of the compositions described herein. In other words, the bioavailability of the Omega-3 fatty acid esters, as measured by the logarithm-transformed AUC, is substantially the same regardless of whether the compositions described herein are administered with or without food. In certain embodiments, the pharmacological effects of administration of compositions described herein are substantially independent of a food effect.

[0101] The term "reduced food effect," as used herein, as used herein, refers to a substantial reduction in the effect of food upon the absorption, following oral administration, of any of the compositions described. In certain embodiments, the compositions described herein have a reduced food effect.

[0102] The term "concomitantly with food" or "administration in the fed state," as used herein, refers to administration from about 30 minutes before a meal to about 1 hour after a meal.

[0103] Various modes of treatment or prevention of medical conditions as described herein are intended to mean "substantial" or "substantially", which includes total but also less than total treatment or prevention, and wherein some biologically or medically relevant result is achieved. A subject, such as a human subject, in need of treatment refers to a subject in need of treatment of a defined disease state or in need of preventative treatment (i.e., prophylaxis) of such a disease state.

[0104] The term "about" or "approximately" as used herein means within an acceptable error range for the particular value as determined by one of ordinary skill in the art, which will depend in part on how the value is measured or determined, i.e., the limitations of the measurement system. Where particular values are described in the

application and claims, unless otherwise stated, the term "about" means within an acceptable error range for the particular value.

[0105] The term “active(s)”, “active ingredient(s)”, “active agents” or “pharmaceutically active ingredient” means a chemical entity intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in a subject.

[0106] The term "functional food" as used herein means any edible or drinkable foods or dietary components (e.g., juices, milk, yogurt, butter, margarine, baking products) that are fortified or enhanced with any of the compositions described herein. The functional food can be, e.g., solid, liquid, semisolid, or a combination thereof. The term "functional food" also encompasses edible and drinkable nutritional supplements.

[0107] The term "hydrophilic-lipophilic balance" or "HLB," as used herein, refers to the relative affinity of a substance or composition for aqueous and oily phases. HLB values can be calculated based on methods and equations known to those of ordinary skill in the art, such as those described in United States Patent 5,585,192. Substances or compositions generally have an average HLB of about 6 to about 20. Hydrophilic-lipophilic balance values can be determined in a variety of the formulas or experimental methods provided, for example, in United States Patent 5,585,192.

[0108] The term “substantially pure” as used herein means at least 90% pure.

PHARMACEUTICAL COMPOSITIONS

[0109] In at least one embodiment, a composition is provided, wherein the composition comprises at least one Omega-3 fatty acid ester, at least one surface active agent, and wherein the composition self-micellizes when in contact with an aqueous medium. In certain embodiments, said at least one Omega-3 fatty acid ester comprises from about 40% (wt/wt) to about 85% (wt/wt) of the composition. In certain embodiments, the at least one Omega-3 fatty acid ester comprises about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80% or 85% (wt/wt) of the composition.

[0110] In certain embodiments, the compositions described herein self-micellize in 0.1N HCl. It is well accepted that 0.1N HCl (simulated gastric fluid), serves as a proxy for the acidity of stomach contents. Accordingly, and without being bound by theory, it is believed that the compositions described herein can self-micellize *in situ* in the stomach or small intestine. In certain embodiments, the compositions described herein more efficiently and effectively deliver Omega-3 fatty acid esters through the intestinal tract when administered with or without food.

[0111] Certain embodiments call for the use of Omega-3 fatty acid esters.

Accordingly, in one aspect, a composition is provided comprising at least one (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid (EPA) ester; or at least one (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA) ester; or a combination thereof, wherein the composition has a ratio of EPA ester to DHA ester of more than 2.0:1.0 to not more than 3.4:1.0 and is substantially free of active ingredients other than said Omega-3 fatty acid esters. In certain embodiments, the Omega-3 fatty acid esters in said composition comprise Omega-3 fatty acid ethyl esters. In certain embodiments, the EPA and DHA esters constitute from at least about 40% to about 95% (wt/wt) of the total Omega-3 fatty acid esters in the composition. In certain embodiments, the EPA and DHA esters comprise about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% (wt/wt) of the total Omega-3 fatty acid esters of the composition.

[0112] It has been discovered that compositions comprising Omega-3 fatty acid esters having a ratio of more than 2.0:1.0 to not more than 3.4:1.0 of alkyl (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17- pentenoate to alkyl (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate (EPA:DHA) are effective for the reduction of TG concentrations in blood serum. In certain embodiments, the EPA and DHA esters comprise at least 40% of the total Omega-3 fatty acid esters of the composition. In certain embodiments, the EPA and DHA esters comprise about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% of the total Omega-3 fatty acid esters of the composition. It also has been discovered that compositions having Omega-3 fatty acid esters including more than about 2.0:1.0 to not more than 3.4:1.0 (EPA:DHA esters) can be formulated with one or more surface active agents to produce compositions that self-micellize in an aqueous medium. The micelles are generally uniformly spherical and stable, and provide for absorption of the Omega-3 fatty acid esters substantially free of any food effect. Based on the observation that the compositions described herein self-micellize in 0.1N HCl, it is believed that the compositions described herein will also self-micellize in the stomach or small intestine. In certain embodiments, such compositions provide beneficial drug delivery profiles for Omega-3 fatty acid esters.

[0113] In certain embodiments, the compositions described herein, comprising EPA and DHA esters, eliminate many of the side effects commonly associated with administration of Omega-3 fatty acid esters. Thus, the compositions described herein, comprising EPA and DHA esters, do not have a bad smell, and/or produce an unpleasant aftertaste, and/or cause burping in the patient. In another aspect, a composition is provided comprising at least one (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid (EPA) ester; or at least one (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-

hexaenoic acid (DHA) ester; or a combination thereof, wherein the composition has a ratio of EPA ester to DHA ester of more than about 2.0:1.0 to not more than about 3.4:1.0, and at least one surface active agent; wherein said EPA ester, DHA ester, or a combination thereof, comprises at least 40% of the total amount of Omega-3 fatty acid esters in said composition. In certain embodiments, the Omega-3 fatty acid esters in said composition comprise Omega-3 fatty acid esters. In certain embodiments, the EPA and DHA esters constitute at least from about 40% to about 95% of the total Omega-3 fatty acid esters of the composition. Accordingly, in certain embodiments, the EPA and DHA esters comprise about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of the total Omega-3 fatty acid esters of the composition.

[0114] In certain embodiments, the ratio of EPA fatty acid ester to DHA ester is from more than 2.0:1.0 to not more than 3.4:1.0. In certain embodiments, the ratio of EPA ester to DHA ester is from about 2.0:1 to about 3.4:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.0:1.0 to about 3.0:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.0:1.0 to about 2.7:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.0:1.0 to about 2.5:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.0:1.0 to about 2.4:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.1:1.0 to about 2.3:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.1:1.0 to about 2.2:1.0. In other embodiments, the ratio of EPA ester to DHA ester is about 2.4:1.0.

[0115] In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.0:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.1:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.15:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.2:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.3:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.4:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.5:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.6:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.7:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.8:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 2.9:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 3.0:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 3.1 1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is

about 3.2:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 3.3:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is about 3.4:1.0.

[0116] In certain embodiments, the compositions described herein comprise an Omega-3 fatty acid ester selected from at least one of the following hexadecatrienoic acid ("HTA" or 16:3 (n-3), or all- Z-7,10,13-hexadecatrienoic acid), a-linolenic acid ("ALA" or 18:3 (n-3), or all-Z-9,12,15- octadecatrienoic acid), stearidonic acid ("SDA" or 18:4 (n-3) or all-Z-6,9,12,15- octadecatetraenoic acid), eicosatrienoic acid ("ETE" or 20:3 (n-3) or all-Z-11, 14, 17 eicosatrienoic acid), eicosatetraenoic acid ("ETA" or 20:4 (n-3), or all-Z-8,11,14,17- eicosatetraenoic acid), eicosapentaenoic acid ("EPA" or 20:5 (n-3) or all-Z-5,8,11,14,17- eicosapentaenoic acid), heneicosapentaenoic acid ("HPA" or 21:5 (n-3) or all-Z-6,9,12,15,18- heneicosapentaenoic acid), docosapentenoic acid ("DPA", or clupanodonic acid or 22:5 (n-3) or all-Z-7,10,13,16,19-docosapentenoic acid); docosahexaenoic acid ("DHA" or 22:6 (n-3) or all-Z-4,7,10,13,16,19-docosahexaenoic acid), tetracosapentenoic acid(24:5 (n-3) or all-Z- 9,12,15,18,21-tetracosapentenoic acid), tetracosahexaenoic acid (nisinic acid or 24:6 (n-3) or all-Z-6,9,12,15,18,21-tetracosahexaenoic acid. In certain embodiments provided herein, the esters comprise an ester of (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17- pentenoic acid (EPA), an ester of (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA), or a combination thereof. In certain embodiments, the esters are ethyl esters. In certain embodiments, the esters are a single Omega-3 fatty acid ester. In certain embodiments, the esters are combinations of different Omega-3 fatty acid esters, such as those recited herein. In certain embodiments, other fatty acids, or dietary oils can also be present.

[0117] In certain embodiments, said Omega-3 fatty acid ester(s) comprise about 40% (wt/wt) of said composition. In certain embodiments, said Omega-3 fatty acid ester(s) comprise at about 45% (wt/wt) of said composition. In certain embodiments, said Omega-3 fatty acid ester(s) comprise about 50% (wt/wt) of said composition. In other embodiments, said Omega-3 fatty acid ester(s) comprise about 55% (wt/wt) of said composition. In other embodiments, said Omega-3 fatty acid ester(s) comprise about 60% (wt/wt) of said composition. In other embodiments, said Omega-3 fatty acid ester(s) comprise about 65% (wt/wt) of said composition. In other embodiments, said Omega-3 fatty acid ester(s) comprise at about 70% (wt/wt) of said composition. In other embodiments, said Omega-3 fatty acid ester(s) comprise about 75% (wt/wt) of said composition. In other embodiments, the Omega-3 fatty acid ester(s) comprise about 80% (wt/wt) of said composition. In other embodiments, the Omega-3 fatty acid ester(s) comprise about 85% (wt/wt) of said composition. In other embodiments, the Omega-3 fatty acid ester(s) comprise about 90% (wt/wt) of said composition. In other

embodiments, the Omega-3 fatty acid ester(s) comprise about 95% (wt/wt) of said composition.

[0118] In certain embodiments, the compositions comprise a pharmaceutical composition comprising a first Omega-3 fatty acid ester selected from the group consisting of an ester of hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentenoic acid, docosahexaenoic acid, tetracosapentenoic acid, tetracosahexaenoic acid, or combinations thereof; and a second Omega-3 fatty acid ester selected from the group consisting of an ester of hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentenoic acid, docosahexaenoic acid, tetracosapentenoic acid, tetracosahexaenoic acid, or combinations thereof and at least one surface active agent. The first and second Omega-3 fatty acid esters to be selected will be different. The ratio of the first to second Omega-3 fatty acid esters should be from more than 2:1 to not more than 3.4:1 (first Omega-3 fatty acid ester:second Omega-3 fatty acid ester). Typically, the ratio of the first to second Omega-3 fatty acid ester is about 2.4:1. The first and second Omega-3 fatty acid esters combined comprise from about 40% to about 85% (wt/wt) of the composition. In certain embodiments, the first and second Omega-3 fatty acid esters combined comprise at least about 40% (wt/wt) of the composition. In certain embodiments, the first and second Omega-3 fatty acid esters combined comprise at least about 45% (wt/wt) of the composition. In certain embodiments, the first and second Omega-3 fatty acid esters combined comprise at least about 50% (wt/wt) of the composition. In certain embodiments, the first and second Omega-3 fatty acid esters combined comprise at least about 55% (wt/wt) of the composition. In certain embodiments, first and second Omega-3 fatty acid esters combined comprise at least about 60% (wt/wt) of the composition. In certain embodiments, the first and second Omega-3 fatty acid esters combined comprise at least about 65% (wt/wt) of the composition. In certain embodiments, the first and second Omega-3 fatty acid esters combined comprise at least about 70% (wt/wt) of the composition. In certain embodiments, first and second Omega-3 fatty acid esters combined comprise at least about 75% (wt/wt) of the composition. In certain embodiments, first and second Omega-3 fatty acid esters combined comprise at least about 80% (wt/wt) of the composition. In certain embodiments, first and second Omega-3 fatty acid esters combined comprise at least about 85% (wt/wt) of the composition. In certain embodiments, these mixed Omega-3 fatty acid ester compositions are substantially free of active ingredients other than said Omega-3 fatty acid esters. These mixed Omega-3 fatty acid ester compositions can further comprise at least one terpene and/or at least one antioxidant. The terpene is typically substantially pure d-limonene and

is present from about 0.1% to about 5% (wt/wt) of said composition. Optionally, the composition can also further comprise natural orange oil from about 0.1% to about 5% (wt/wt) of said composition. The at least one surface active agent can be any one or more of the surface active agents described herein, but is typically a polysorbate and/or a poloxamer, such as for example, polysorbate 80 and Pluronic F87. The surface active agent is present from about 15% to about 31% (wt/wt) of the composition. The antioxidant(s) suitable for use in these mixed Omega-3 fatty acid ester compositions, include, but are not limited to tocopherols and/or tocotrienols and can be present from about 0.01% to about 5% (wt/wt) of the composition. In certain such embodiments, the tocopherols and/or tocotrienols can be present at about 0.01%, 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5% by weight of the compositions. In certain such embodiments, the antioxidant is a tocopherol present at about 0.4% by weight of the composition.

[0119] In certain embodiments, compositions comprise an Omega-3 fatty acid ester, such as an ethyl ester, one or more surface active agents. In certain embodiments, said surface active agent is selected from the group consisting of nonionic surface active agents, cationic surface active agents, anionic surface active agents, zwitterionic surface active agents, or combinations thereof. In some embodiments, the compositions include one or more non-ionic surface active agents. Non-ionic surface active agents generally have a hydrophobic group and a reactive hydrogen atom, for example aliphatic alcohols, acids, amides and alkyl phenols, with alkylene oxides, especially ethylene oxide either alone or in combination with propylene oxide. Examples of nonionic surfactant compounds include, but are not limited to, polyoxyethylene glycol sorbitan alkyl esters, block copolymers of polyethylene glycol and polypropylene glycol, ethylene glycol fatty acid esters, poly(ethylene glycol) fatty acid esters, propylene glycol fatty acid esters, poly(propylene glycol) fatty acid esters, glycol fatty acid esters, trimethylolpropane fatty acid esters, pentaerythritol fatty acid esters, glucoside derivatives, glycerin alkyl ether fatty acid esters, trimethylolpropane oxyethylene alkyl ethers, fatty acid amides, alkylolamides, alkylamine oxides, lanolin and its derivatives, castor oil derivatives, hardened castor oil derivatives, sterols and its derivatives, polyoxyethylene alkyl ethers, polyoxyethylene alkyl allyl ethers, polyoxyethylene alkylamine, polyoxyethylene fatty acid amides, polyoxyethylene alkylolamides, polyoxyethylene diethanolamine fatty acid esters, polyoxyethylene trimethylolpropane fatty acid esters, polyoxyethylene alkyl ether fatty acid esters, polyoxyethylene polyoxypropylene glycols, polyoxyethylene polyoxypropylene alkyl ethers, polyoxyethylene polyoxypropylene polyhydric alcohol ethers, glycerin fatty acid esters, polyglycerin fatty acid esters, polyoxyethylene glycerin fatty acid esters, sorbitan fatty acid esters, polyoxyethylene sorbitan fatty acid esters,

sucrose fatty acid esters, or combinations thereof.

[0120] In certain embodiments, the surface active agents comprise polyoxyethylene glycol sorbitan alkyl esters, block copolymers of polyethylene glycol and polypropylene glycol, or combinations thereof.

[0121] Examples of polyoxyethylene glycol sorbitan alkyl esters are typically the polysorbates. Polysorbates are a class of oily liquids derived from PEG-ylated sorbitan (a derivative of sorbitol) esterified with fatty acids. Common brand names for polysorbates include Tween®. Tween-20, Tween-60 and Tween-80, for example, are available from AkzoNobel (Strawinskylaan 2555 1077 ZZ, Amsterdam, the Netherlands). Exemplary polysorbates include polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate), and polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

[0122] Examples of block copolymers of polyethylene glycol and polypropylene glycol include the poloxamers. Poloxamers are nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). Certain poloxamers, such as those listed herein, are also known by the trade names Pluronic® available from suppliers such as BASF AG (Ludwigshafen, Germany). Because the lengths of the polymer blocks can be customized, many different poloxamers exist that have slightly different properties. Further exemplary Pluronic poloxamers include, but are not limited to Pluronic® 10R5, Pluronic® 17R2, Pluronic® 17R4, Pluronic® 25R2, Pluronic® 25R4, Pluronic® 31R1, Pluronic® F 108 Cast Solid Surfacta, Pluronic® F 108 NF, Pluronic® F 108 Pastille, Pluronic® F 108 Prill, Pluronic® F 108NF Prill Poloxamer 338, Pluronic® F 127, Pluronic® F 127 Prill, Pluronic® F 127 NF, Pluronic® F 127 NF 500 BHT Prill, Pluronic® F 127 NF Prill Poloxamer 407, Pluronic® F 38, Pluronic® F 38 Pastille, Pluronic® F 68, Pluronic® F 68 Pastille, Pluronic® F 68 LF Pastille, Pluronic® F 68 NF, Pluronic® F 68 NF Prill Poloxamer 188, Pluronic® F 68 Prill, Pluronic® F 68 Prill, Pluronic® F 77, Pluronic® F 77 Micropastille, Pluronic® F 87, Pluronic® F 87 NF, Pluronic® F 87 NF Prill Poloxamer 237, Pluronic® F 87 Prill, Pluronic® F 88, Pluronic® F 88 Pastille, Pluronic® F 88 Prill, Pluronic® F 98, Pluronic® F 88 Prill, Pluronic® F 98, Pluronic® F 98 Prill, Pluronic® L 10, Pluronic® L 101, Pluronic® L 121, Pluronic® L 31, Pluronic® L 35, Pluronic® L 43, Pluronic® L 44, Pluronic® L 61, Pluronic® L 62, Pluronic® L 62 LF, Pluronic® L 62D, Pluronic® L 64, Pluronic® L 81, Pluronic® L 92, Pluronic® L44 NF INH surfactant Poloxamer 124, Pluronic® N 3, Pluronic® P 103, Pluronic® P 104, Pluronic® P 105, Pluronic® P 123 Surfactant, Pluronic® P 65, Pluronic® P 84, Pluronic® P 85, or combinations thereof.

[0123] In certain embodiments, the composition comprises from about 15% (wt/wt) to about 31% (wt/wt) polysorbate. In certain embodiments, said polysorbate is polysorbate 80. In other embodiments, the composition comprises from about 0.5% (wt/wt) to about 5% (wt/wt) poloxamer. In certain embodiments, the polysorbate is polysorbate 20, polysorbate 60, polysorbate 80 or a combination thereof, and the poloxamer is Pluronic F 87, Pluronic L61, Pluronic F 127, or a combination thereof. In some embodiments, the composition comprises Omega-3 fatty acid esters, such as ethyl esters, in an amount from about 50% (wt/wt) to about 80% (wt/wt); and polysorbate from about 15% (wt/wt) to about 99% (wt/wt); and poloxamer from about 0.05% (wt/wt) to about 50% (wt/wt). In certain embodiments, the at least one surface active agent is a combination of a polysorbate, such as for example polysorbate 80, from about 15% (wt/wt) to about 31% (wt/wt) of said composition, and a poloxamer, such as for example Pluronic F87, from about 0.5% (wt/wt) to about 5% (wt/wt) of said composition,.

[0124] In certain embodiments, said polysorbate comprises about 15% (wt/wt) to about 70% (wt/wt) of said composition. In certain embodiments, said polysorbate comprises about 15% (wt/wt) to about 50% (wt/wt) of said composition. In certain embodiments, said polysorbate comprises about 15% (wt/wt) to about 31% (wt/wt) of said composition. In certain embodiments, said polysorbate comprises about 15% (wt/wt) to about 25% (wt/wt) of said composition. In certain embodiments, said polysorbate comprises about 15% (wt/wt) to about 20% (wt/wt) of said composition. In certain embodiments, said polysorbate comprises about 20% (wt/wt) to about 31% (wt/wt) of said composition.

[0125] In certain embodiments, the poloxamer comprises from about 0.5% (wt/wt) to about 5% (wt/wt) of said composition. In certain embodiments, the poloxamer comprises from about 0.5% (wt/wt) to about 4% (wt/wt) of said composition. In certain embodiments, the poloxamer comprises from about 0.5% (wt/wt) to about 3% (wt/wt) of said composition. In certain embodiments, the poloxamer comprises from about 0.5% (wt/wt) to about 2% (wt/wt) of said composition. In certain embodiments, the poloxamer comprises from about 0.5% (wt/wt) to about 1% (wt/wt) of said composition.

[0126] In some embodiments, the compositions include one or more anionic surface active agents. Exemplary "anionic surface active agents" include, but are not limited to, N-acyl-L-glutamic acid diethanolamine, N-acyl-L-glutamic acid triethanolamine, sodium N-acyl-L-glutamate, sodium alkanesulfonate, ammonium alkyl (C12, C14, C16) sulfate, alkyl (C11, C13, C15) sulfuric acid triethanolamine, alkyl (C11, C13, C15) sulfuric acid triethanolamine, alkyl (C12 to C14) sulfuric acid triethanolamine, liquid alkylsulfuric acid triethanolamine, sodium alkyl (C12, C13) sulfate, liquid sodium alkylsulfate, sodium isoethionate, sodium lacto-isostearate, disodium undecylenoylamido

ethyl sulfosuccinate, triethanolamine sulfooleate, sodium sulfooleate, disodium oleamide sulfosuccinate, potassium oleate, sodium oleate, morpholine oleate, oleoyl sarcosine, oleoyl methyltaurine sodium salt, potassium-containing soap base, liquid base for potassium soap, potassium soap, carboxylated polyoxyethylene tridodecyl ether, sodium salt (3 ethyle oxide "E.O.") of carboxylated polyoxyethylene tridodecyl ether, triethanolamine N-hydrogenated tallow fatty-acyl-L-glutamate, sodium N-hydrogenated tallow fatty-acyl- L-glutamate, sodium hydrogenated coconut fatty acid glyceryl sulfate, sodium diundecylenoylamido ethyl sulfosuccinate, sodium stearyl sulfate, potassium stearate, triethanolamine stearate, sodium stearate, sodium N-stearoyl-L-glutamate, disodium stearoyl- L-glutamate, stearoyl methyltaurine sodium salt, sodium dioctyl sulfosuccinate, liquid sodium dioctyl sulfosuccinate, liquid disodium polyoxyethylene monooleylamido sulfosuccinate (2 E.O.), disodium polyoxyethylene lauroyl ethanolamide sulfosuccinate (5 E.O.), disodium lauryl sulfosuccinate, diethanolamide cetyl sulfate, sodium cetyl sulfate, soap base, sodium cetostearyl sulfate, triethanolamine tridecyl sulfate, potassium palmitate, sodium palmitate, palmitoyl methyltaurine sodium salt, liquid castor oil fatty acid sodium salt (30%), ammonium polyoxyethylene alkyl ether sulfate (3 E.O.), liquid diethanolamine polyoxyethylene alkyl (C12, C13) ether sulfate, liquid triethanolamine polyoxyethylene alkyl ether sulfate (3 E.O.), triethanolamine polyoxyethylene alkyl (C11, C13, C15) ether sulfate (1 E.O.), triethanolamine polyoxyethylene alkyl (C12, C13) ether sulfate (3 E.O.), liquid sodium polyoxyethylene alkyl ether sulfate (3 E.O.), sodium polyoxyethylene alkyl (C11, C13, C15) ether sulfate (1 E.O.), sodium polyoxyethylene alkyl (C11 to C15) ether sulfate (3 E.O.), sodium polyoxyethylene alkyl (C12, C13) ether sulfate (3 E.O.), sodium polyoxyethylene alkyl (C12 to C14) ether sulfate (3 E.O.), sodium polyoxyethylene alkyl (C12 to C15) ether sulfate (3 E.O.), disodium polyoxyethylene alkyl (C12 to C14) sulfosuccinate (7 E.O.), sodium polyoxyethylene undecyl ether sulfate, liquid sodium polyoxyethylene octyl phenyl ether sulfate, ammonium polyoxyethylene oleyl ether sulfate, disodium polyoxyethylene lauryl sulfosuccinate, sodium polyoxyethylene nonyl phenyl ether sulfate, sodium polyoxyethylene pentadecyl ether sulfate, triethanolamine polyoxyethylene myristyl ether sulfate, sodium polyoxyethylene myristyl ether sulfate, sodium polyoxyethylene myristyl ether sulfate (3 E.O.), liquid sodium polyoxyethylene lauryl ether acetate (16 E.O.), ammonium polyoxyethylene lauryl ether sulfate (2 E.O.), triethanolamine polyoxyethylene lauryl ether sulfate, sodium polyoxyethylene lauryl ether sulfate, diethanolamine myristyl sulfate, sodium myristyl sulfate, potassium myristyl sulfate, sodium N- myristoyl- L-glutamate, sodium myristoylmethylaminoacetate, liquid myristoyl methyl- -alanine sodium salt, myristoyl methyltaurine sodium salt, medicinal soaps, triethanolamine/magnesium coco alkyl

sulfate, triethanolamine N-coconut oil fatty-acyl-L-glutamate, sodium N-coconut oil fatty-acyl-L-glutamate, sodium coconut oil fatty acid ethyl ester sulfonate, coconut oil fatty acid potassium salt, liquid coconut oil fatty acid potassium salt, sodium N-coconut oil fatty/hydrogenated fatty-acyl-L-glutamate, coconut oil fatty acid sarcosine, coconut oil fatty acid sarcosine triethanolamine salt, coconut oil fatty acid sarcosine sodium salt, coconut oil fatty acid triethanolamine salt, liquid triethanolamine salt of coconut oil fatty acid, coconut oil fatty acid sodium salt, coconut oil fatty acid methyl alanine sodium salt, liquid coconut oil fatty acid methyl alanine sodium salt, coconut oil fatty acid methyltaurine potassium salt, coconut oil fatty acid methyltaurine sodium salt, sodium laurylamino dipropionate, liquid sodium laurylamino dipropionate (30%), sodium lauryl sulfoacetate; sodium lauryl benzenesulfonate, lauryl sulfate, ammonium lauryl sulate, potassium lauryl sulfate, diethanolamine lauryl sulfate, triethanolamine lauryl sulfate, sodium lauryl sulfate, magnesium lauryl sulfate, monoethanolainine lauryl sulfate, potassium laurate, lauric acid triethanolamine, liquid lauric acid triethanolamine, sodium laurate, lauric acid/myristic acid triethanolamine, lauroyl-L-glutamic acid triethanolamine, sodium N- lauroyl-L-glutamate, lauroyl sarcosine, lauroyl sarcosine potassium, liquid lauroyl sarcosine triethanolamine salt, lauroyl sarcosine sodium, liquid lauroyl methyl-.beta.-alanine sodium salt, lauroyl methyltaurine sodium salt, liquid lauroyl methyltaurine sodium salt, or combinations thereof.

[0127] In certain embodiments, said anionic surfactant(s) comprise about 0.05% (wt/wt) to about 25% (wt/wt) of said composition. In certain embodiments, said anionic surfactant(s) comprise about 0.05% (wt/wt) to about 15% (wt/wt) of said composition. In certain embodiments, said anionic surfactant(s) comprise about 0.05% (wt/wt) to about 5% (wt/wt) of said composition. In certain embodiments, said anionic surfactant(s) comprise about 0.5% (wt/wt) to about 3% (wt/wt) of said composition. In certain embodiments, said anionic surfactant(s) comprise about 0.7% (wt/wt) of said composition. In certain embodiments, said anionic surfactant(s) comprise sodium lauryl sulfate.

[0128] In certain embodiments, compositions comprise an Omega-3 fatty acid ester, such as an ethyl ester, and further comprise one or more surface active agents. In certain embodiments, said surface active agent is selected from the group consisting of a polysorbate or a combination of polysorbates, and an anionic surfactant or a combination of anionic surfactants, or a combination of said polysorbates and said anionic surfactants. In other embodiments, the composition comprises from about 15% (wt/wt) to about 31% (wt/wt) polysorbate. In certain embodiments, said polysorbate is polysorbate 80. In other embodiments, the composition comprises from about 0.5% (wt/wt) to about 5% (wt/wt) anionic surfactant(s). In certain embodiments, the polysorbate is polysorbate 80,

polysorbate 20, or a combination thereof, and the anionic surfactant is sodium lauryl sulfate. In some embodiments, the composition comprises Omega-3 fatty acid esters, such as ethyl esters, in an amount from about 40% (wt/wt) to about 85% (wt/wt); and polysorbate from about 15% (wt/wt) to about 99% (wt/wt); and anionic surfactant(s) from about 0.05% (wt/wt) to about 50% (wt/wt). In some embodiments, the composition comprises Omega-3 fatty acid esters, such as ethyl esters, in an amount from about 50% (wt/wt) to about 80% (wt/wt) (90); and polysorbate from about 15% (wt/wt) to about 99% (wt/wt); and anionic surfactant(s) such as, for example, sodium lauryl sulfate from about 0.05% (wt/wt) to about 2% (wt/wt). In some embodiments, the composition comprises about 0.7% (wt/wt) sodium lauryl sulfate.

[0129] In certain embodiments, said poloxamer comprises about 0.05% (wt/wt) to about 25% (wt/wt) of said composition. In certain embodiments, said poloxamer comprises about 0.05% (wt/wt) to about 15% (wt/wt) of said composition. In certain embodiments, said poloxamer comprises about 0.05% (wt/wt) to about 5% (wt/wt) of said composition. In certain embodiments, said poloxamer comprises about 0.5% (wt/wt) to about 3% (wt/wt) of said composition.

[0130] In some embodiments, the compositions include additional surface active agents such as the zwitterionic and cationic surface active agents. Examples of such surface active agents include, but are not limited to the bile acids (e.g., cholic acid, chenodeoxycholic acid, glycocholic acid, glycodeoxycholic acid, taurocholic acid, taurochenodeoxycholic acid, taurolithocholic acid, deoxycholic acid, lithocholic acid, and ursodeoxycholic acid and salts thereof, e.g., sodium, potassium, lithium), natural emulsifiers (e.g. acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), long chain amino acid derivatives, high molecular weight alcohols (e.g. stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (e.g. carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (e.g. carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose), polyoxyethylene esters (e.g. polyoxyethylene monostearate [Myrj 45], polyoxyethylene hydrogenated castor oil, polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (e.g. Cremophor), polyoxyethylene ethers, (e.g. polyoxyethylene lauryl ether [Brij 30]), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyllaurate, sodium lauryl sulfate, cetrimonium bromide, cetylpyridinium chloride,

benzalkonium chloride, docusate sodium or combinations thereof.

[0131] Compositions suitable for self-micellization as described herein generally have an HLB from about 12 to about 18. In certain embodiments, said compositions have an HLB from about 12.0 to about 14.0. In certain embodiments, said compositions have an HLB from about 13.0 to about 14.0. In certain embodiments, said compositions have an HLB from about 13.5 to about 13.8. The total HLB of all the surface active agents or surfactants used in the composition is generally from about 12 to about 18. In some embodiments, the total HLB of all surface active agents used in the composition is generally from about 12 to about 15. In some embodiments, the total HLB of all surface active agents or surfactants used in the composition is generally from about 13 to about 15.

[0132] In certain embodiments, the at least one surface active agent or surfactant has a HLB of at least 8.0. In some embodiments, said surface active agent(s) or surfactant(s) have a combined HLB in the range of from about 13 to about 15. As the HLB value of the surface active agent(s) or surfactant(s) increases, the amount of surface active agent or surfactant needs to be decreased, such that at an HLB of 17, only about 25% (wt/wt) to about 42% (wt/wt) of surface active agent(s) or surfactant(s) may be required.

[0133] In certain embodiments, the composition further comprises a terpene. In certain embodiments, the terpene is d-limonene. In one embodiment, the terpene is a cyclic terpene. In one embodiment, the terpene is d-limonene ((+)-limonene), which is the (R)-enantiomer. In one embodiment, the terpene is L-limonene, which is the (S)-enantiomer. In one embodiment, the terpene is racemic limonene, known as dipentene. In another embodiment, the terpene is a terpenoid. In another embodiment, the terpene or terpenes are derived from a natural oil (e.g., a citrus oil such as orange oil). Other terpenes are contemplated, such as monoterpenes (e.g., terpinenes, terpinolenes, phellandrenes, or menthol), having structures that are similar to d-limonene. In certain embodiments, the compositions further comprise substantially pure d-limonene from about 0.1% to about 5% by weight of the composition. In certain other embodiments, the compositions further comprise natural orange oil from about 0.1% to about 5% by weight of the composition. Compositions comprising d-limonene or orange oil can aid in the elimination and/or minimization of side effects from the oral administration of Omega-3 fatty acid esters. Such side effects include regurgitation, frequency of belching, gastroesophageal reflux disease (GERD), bloating, increased intestinal gas, fish taste, fishy breath, fish smell, nausea, diarrhea, or combinations thereof.

[0134] In other embodiments, the composition further comprises an antioxidant. In certain embodiments, the antioxidant is selected from the consisting of at least one

tocopherol, at least one tocotirenol, or combinations thereof. In other embodiments, the compositions described herein may include one or more tocopherol(s). In embodiments further comprising the at least one or more antioxidant(s), the antioxidant(s) can be present from about 0.01% to about 5% by weight of the compositions. In such embodiments, the antioxidant(s) can be present at about 0.01%, 0.05%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 1.5%, 2%, 2.5%, 3%, 3.5%, 4%, 4.5% or 5% by weight of the compositions. In certain embodiments, the antioxidant(s) can be present at about 0.4% by weight of the compositions.

[0135] In an at least one additional embodiment, compositions comprising micelles are provided, wherein the micelles are formed by the addition of an aqueous medium to a composition of any one of the embodiments provided herein prior to administration of said composition to a subject in need of treatment. Alternatively, micelles can also be formed when the compositions are added to an aqueous medium. In certain embodiments, the micelles have a diameter of up to about 10 μm. In other embodiments, substantially all of the micelles have an average diameter of from about 1 μm to about 10 μm. In certain embodiments, the micelles have an average diameter of about 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 μm. In certain embodiments, said micelles are stable at room temperature. In certain embodiments, the composition forms micelles in an aqueous medium having an acidic pH. In certain other embodiments, the compositions form micelles in 0.1N HCl.

[0136] In another embodiment, a composition is provided, wherein said composition comprises at least one (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid (EPA) ester and at least one (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid (DHA) ester, and wherein said composition has a ratio of EPA ester to DHA ester of more than 2.0:1.0 to not more than about 3.4:1.0, provided that the concentration of said EPA ester, DHA ester, or a combination thereof comprises from about 40% to about 85% by weight of the total amount of Omega 3 esters in said composition. In certain embodiments, the ratio of EPA ester to DHA ester is from about 2.0:1.0 to about 2.5:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.1:1.0 to about 2.4:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.1:1.0 to about 2.3:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.1:1.0 to about 2.2:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is 2.4:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.0:1.0 to about 3.3:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.2:1.0 to about 3.2:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.4:1.0 to about 3.1:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.5:1.0 to about

3.0:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.6:1.0 to about 2.9:1.0. In other embodiments, the ratio of EPA ester to DHA ester is from about 2.7:1.0 to about 2.8:1.0. In certain embodiments, said ratio of EPA ester to DHA ester in said composition is more than 2.0:1.0.

[0137] In certain embodiments, the Omega-3 fatty acid esters used herein are substantially pure. In certain embodiments, the Omega-3 fatty acid esters are from about 80% to about 99% pure. In certain embodiments, the Omega-3 fatty acid esters are at least 80%, 85%, 90%, 92%, 94%, 96%, 98% or 99% pure.

METHODS FOR TREATING CARDIOVASCULAR CONDITIONS OR DISORDERS

[0138] Methods are provided of treating one or more cardiovascular condition or disorder in a subject in need of treatment, which method comprises administering to said subject a therapeutically effective amount of a composition of any one of the embodiments provided herein, or a micelle of any one of the embodiments provided herein.

[0139] Accordingly, in certain embodiments, the cardiovascular condition or disorder is of the heart and vasculature, including, for example, hypertension, hyperlipidemia, hypertriglyceridemia, atherosclerosis, transient ischemic attack, systolic dysfunction, diastolic dysfunction, aneurysm, aortic dissection, myocardial ischemia, acute myocardial infarction (AMI), acute ST-segment elevation myocardial infarction (STEMI), acute non-ST -segment elevation myocardial infarction (NSTEMI), angina pectoris, unstable angina (UA), and stable angina (SA), myocardial infarction, congestive heart failure, dilated congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, corpulmonale, arrhythmia, valvular heart disease, endocarditis, pulmonary embolism, venous thrombosis, peripheral vascular disease, and peripheral artery disease.

[0140] In particular embodiments, the cardiovascular condition or disorder is hypertension, hyperlipidemia, or a combination thereof. In other embodiments, the cardiovascular condition or disorder is hypertriglyceridemia.

[0141] In another embodiment, a method is provided for treating moderate to severe hypertriglyceridemia in a subject in need thereof, wherein the method comprises providing a subject having a fasting baseline TG level of about 200 mg/dL to about 500 mg/dL and administering to the subject a composition as described herein. In one embodiment, the composition can be administered in a daily amount of from about 0.5 g to about 1 g, from about 1 g to about 2 g, from about 2 g to about 4 g, from about 4 g to

about 6 g, or from about 6 g to about 10 g.

[0142] In certain embodiments, the amount of total fasting TG in the subject's blood serum is reduced by at least 20% within thirty days of administration of said composition or said micelles in a subject having at least 150 mg/dL fasting blood serum TG at the start of the dosing regimen. In other embodiments, the total concentration of low-density lipoprotein (LDL) in said subject's blood serum does not substantially increase within thirty days of administration of said composition or said micelles. In certain embodiments, the therapeutically effective amount of said composition or said micelles comprises at least 0.5 g/day of the Omega-3 fatty acid esters. In other embodiments, said subject's blood serum has a concentration of at least 20 nmol/mL of combined EPA, DHA or combinations thereof within four hours after administration of said composition or said micelles.

[0143] In further embodiments, a method is provided of administering to a subject a composition comprising at least one Omega-3 fatty acid ester wherein the ratio of high-density lipoprotein is increased relative to LDL in the blood serum of the subject. In certain embodiments, the administration is an oral administration. In certain embodiments, the subject is a human.

[0144] Some embodiments provide for a method of administering to a subject a composition comprising at least one Omega-3 fatty acid ester and at least one surface active agent, wherein said at least one Omega-3 fatty acid ester self-micellizes when in contact with an aqueous medium, and said at least one Omega-3 fatty acid ester when orally administered is absorbed by said subject at a rate that is substantially independent of a food effect. In certain embodiments, the reduction of the food effect may yield a reduction in F of at least 30%, at least 40%, at least 50%, or at least 75%.

[0145] A method is provided of administering to a subject a composition comprising at least one Omega-3 fatty acid ester and at least one surface active agent, wherein said at least one Omega-3 fatty acid ester self-micellizes when in contact with an aqueous medium, and said at least one Omega-3 fatty acid ester when orally administered is absorbed by said subject at a rate that is substantially independent of a food effect. In certain embodiments, said composition is a composition of any one of the embodiments provided herein. In other embodiments, at least 0.5 g/day of the Omega-3 fatty acid ester is administered to said subject.

[0146] In another embodiment, the composition as described herein is administered, 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. In another embodiment, the composition as described herein is administered for an unlimited period of time to a subject in need of chronic treatment.

[0147] In other embodiments, said subject's blood serum has a concentration of at least 20 nmol/mL of said at least one Omega-3 fatty acid ester within four hours after administration of said composition. In other embodiments, said subject's blood serum has a concentration of at least 50 nmol/mL of said at least one Omega-3 fatty acid ester within four hours after administration of said composition. In other embodiments, said subject's blood serum has a concentration of at least 100 nmol/mL of said at least one Omega-3 fatty acid ester within four hours after administration of said composition. In other embodiments, the concentration of said at least one Omega-3 fatty acid ester in said subject's blood serum can be increased upon the administration of increasing doses of said composition.

[0148] In certain embodiments, a method is provided of minimizing and/or eliminating side effects from the oral administration of Omega-3 fatty acid esters in the presence of a surface active agent to a subject in need of treatment comprising administering a composition of any one of the embodiments provided herein or the micelles of any one of the embodiments provided herein. In certain embodiments, the method of minimizing side effects eliminates the onset of side effects. In some embodiments, non-limiting examples of the side effects include regurgitation, frequency of belching, gastroesophageal reflux disease (GERD), bloating, increased intestinal gas, fish taste, fishy breath, fish smell, nausea, diarrhea, or combinations thereof.

[0149] In certain embodiments, a method is provided of minimizing and/or eliminating side effects from the oral administration of Omega-3 fatty acid esters in the presence of at least one terpene or natural orange oil to a subject in need of treatment comprising administering a composition of any one of the embodiments provided herein or the micelles of any one of the embodiments provided herein. In certain embodiments, the at least one terpene is typically, but not necessarily d-limonene that is at least 95% pure. In certain embodiments, the method of minimizing side effects eliminates the onset of side effects. In some embodiments, non-limiting examples of the side effects include regurgitation, frequency of belching, gastroesophageal reflux disease (GERD), bloating, increased intestinal gas, fish taste, fishy breath, fish smell, nausea, diarrhea, or combinations thereof.

[0150] Some embodiments provide for a method of reducing a food effect in a subject in need of treatment, which method comprises administering to a human subject a therapeutically effective amount of any one of the compositions described herein. In certain embodiments, the food effect is substantially eliminated.

[0151] Methods are also provided for improving patient compliance during the

oral administration of Omega-3 fatty acid esters to a subject in need of treatment comprising administering a composition as described herein.

[0152] The compositions described herein can be administered to a human subject in need of such administration with a non-Omega-3 fatty acid ester lipid-lowering or cholesterol lowering agent selected from the group consisting of cholesterol absorption inhibitors, bile acid sequestrants/resins, statins, niacin and derivatives, MTP inhibitors, fibrates and CETP inhibitors. These lipid-lowering or cholesterol lowering agents can be categorized by their mechanism of action. For example, cholesterol absorption inhibitors inhibit absorption of dietary cholesterol and inhibit reabsorption of biliary cholesterol. Examples of cholesterol absorption inhibitors include, but are not limited to, phytosterols, ezetimibe, and (3R,4S)-1,4-bis(4-methoxyphenyl)-3-(3-phenylpropyl)-2-azetidinone (SCH 48461). Bile acid sequestrants/resins are polymeric compounds and function as ion exchange resins. Bile acid sequestrants exchange anions such as chloride ions for bile acids. By doing so, they bind bile acids and sequester them from enterohepatic circulation. Since bile acid sequesterants are large polymeric structures, they are not well-absorbed from the gut into the bloodstream. Thus, bile acid sequestrants, along with any bile acids bound to the drug, are excreted via the feces after passage through the gastrointestinal tract. Examples of bile acid sequestrants/resins include, but are not limited to cholestyramine, colesevelam, and colestipol. Statins are a class of compounds that inhibit the enzyme HMG-CoA reductase. Examples of statins include, but are not limited to rosuvastatin, lovastatin, fluvastatin, simvastatin, pravastatin, and atorvastatin. It is believed that niacin and its derivatives function by stimulating the G-protein coupled receptor GPR109A, which causes the inhibition of fat breakdown in adipose tissue. Examples of niacin and its derivatives include, but are not limited to, niceritrol, niacin, nicofuranose, aluminium nicotinate, nicotinyl alcohol, and acipimox. MTP (Microsomal Triglyceride Transfer Protein) is a lipid transfer protein that is required for the assembly and secretion of very low density lipoproteins by the liver and chylomicrons by the intestine. Accordingly, inhibitors of MTP decrease levels of plasma LDL-C. Examples of MTP inhibitors include, but are not limited to, lomitapide for human use and dirlotapide and mitrapatide for veterinary use in dogs. Rodent and human studies suggest that fibrates exert their hypolipidemic effects via several mechanisms. Examples of fibrates include, but are not limited to bezafibrate, ciprofibrate, clofibrate, gemfibrozil, and fenofibrate. CETP (Cholesterylester Transfer Protein) inhibitors improve blood plasma lipid profiles by increasing HDL ("good" cholesterol containing particle) and decreasing LDL ("bad" cholesterol containing particle). Examples of CETP inhibitors include, but are not limited to anacetrapib and evacetrapib.

[0153] In addition to the aforementioned disease states, several other conditions

or disorders can also benefit from treatment with the compositions described herein, such as for example; metabolic syndrome; macular degeneration (AREDS2 Research Group et. al. The Age-Related Eye Disease 2 (AREDS2): study design and baseline characteristics (AREDS2 report number 1), Opthalmology. 2012 Nov. 119(11):2282-9. doi 10.1016/j.optha 2012.05.027. Epub 2012 Jul 26; SanGiovanni JP et.al., ω-3 long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: AREDS report 30, a prospective cohort study from the Age-Related Eye Disease Study. Am. J. Clin. Nutr. 2009; 90:1601-70.); cognitive impairment resulting from surgery or traumatic brain injury, such as for example resulting from a concussion (Lewis M. et. al. Therapeutic use of omega-3 fatty acids in severe head trauma. Am J Emerg Med. 2013 Jan;31(1):273.e5-8. doi: 10.1016/j.ajem.2012.05.014. Epub 2012 Aug 3; Mills JD. et. al. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. Neurosurgery. 2011 Feb;68(2):474-81; discussion 481. doi: 10.1227/NEU.0b013e3181ff692b.); major depression, suicide, post-partum depression (Logan AC. Omega-3 fatty acids and major depression: a primer for the mental health professional. Lipids Health Dis. 2004 Nov 9;3:25; Lewis MD et al. Suicide deaths of active-duty US military and omega-3 fatty-acid status: a case-control comparison. J Clin Psychiatry. 2011 Dec;72(12):1585-90. doi: 10.4088/JCP.11m06879. Epub 2011 Aug 23; Makrides M. et. al. Docosahexaenoic acid and post-partum depression - is there a link? Asia Pac J Clin Nutr. 2003;12 Suppl:S37.); inflammation (Kelley DS et. al. DHA supplementation decreases serum C-reactive protein and other markers of inflammation in hypertriglyceridemic men. J Nutr. 2009 Mar;139(3):495-501. doi: 10.3945/jn.108.100354. Epub 2009 Jan 21.); primary sclerosing cholangitis (Martin CR. et. al. The safety and efficacy of oral docosahexaenoic acid supplementation for the treatment of primary sclerosing cholangitis - a pilot study. Aliment Pharmacol Ther. 2012 Jan;35(2):255-65. doi: 10.1111/j.1365-2036.2011.04926.x. Epub 2011 Nov 30.), borderline personality disorder in women (Zanarini MC et al. Omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. Am J Psychiatry. 2003 Jan;160(1):167-9.), breast cancer (Bougnoux P. et al. Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid: a phase II trial. Br J Cancer. 2009 Dec 15;101(12):1978-85. doi: 10.1038/sj.bjc.6605441. Epub 2009 Nov 17.), non-alcoholic fatty acid liver disease (Parker HM. et. al. Omega-3 supplementation and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol. 2012 Apr;56(4):944-51. doi: 10.1016/j.jhep.2011.08.018. Epub 2011 Oct 21; Nobili V. Docosahexaenoic acid for the treatment of fatty liver: Randomised controlled trial in children. Nutr Metab Cardiovasc

Dis. 2012 Dec 7. pii: S0939-4753(12)00256-6. doi: 10.1016/j.numecd.2012.10.010. [Epub ahead of print]; Christopher M.D. et. al. Menhaden oil decreases high-fat diet-induced markers of hepatic damage, steatosis, inflammation, and fibrosis in obese Ldlr-/- mice. J Nutr. 2012 Aug;142(8):1495-503. doi: 10.3945/jn.112.158865. Epub 2012 Jun 27.), and improvement in cognition and behavior in children (Richardson AJ. et. al. Docosahexaenoic acid for reading, cognition and behavior in children aged 7-9 years: a randomized, controlled trial (the DOLAB Study). PLoS One. 2012;7(9):e43909. doi: 10.1371/journal.pone.0043909. Epub 2012 Sep 6.). These conditions or disorders can be treated by administering the compositions described herein to a subject, typically a human, in need of such administration.

KITS

[0154] Packaged pharmaceutical kits are included herein. The kits comprise compositions described herein as unit dosage forms in a container and instructions for using the dosage form to treat a subject having a disease or disorder responsive to treatment by administration of the dosage forms comprising the compositions described herein.

[0155] The packaged pharmaceutical kits provide prescribing information, over the counter medical use information, and/or nutritional information for the dosage form including, for example and without limitation, to a subject or health care provider, or as a label in a packaged pharmaceutical kit. Information included in the kit may include, for example and without limitation, efficacy, dosage and administration, contraindication and adverse reaction information pertaining to the Omega-3 fatty acid dosage form. The dosage and administration information, for example, can include dosing frequency as well as administration of the compositions with or without food.

[0156] In certain embodiments the dosage forms comprising the compositions provided herein are in the form of liquid or capsules provided either as blister packages or in bottles together with over the counter medical use information and/or nutritional information.

[0157] The packaged pharmaceutical kits can comprise one or more of the compositions described herein as the only active ingredient. In other embodiments, one or more of the compositions described herein can be packaged in combination with one or more active agents other than a non-Omega 3 ester, such as for example and without limitation, one or more other lipid lowering or cholesterol lowering agents selected from the group consisting of cholesterol absorption inhibitors, bile acid sequestrants/resins, statins, niacin and derivatives, MTP inhibitors, fibrates and CETP inhibitors.

DOSAGE FORMS

[0158] Any of the compositions provided herein comprising at least one Omega-3 fatty acid ester can be provided as a pharmaceutical composition, a nutraceutical formulation, or a dietary supplement.

[0159] The pharmaceutical compositions described herein may further include one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients include, but are not limited to, carriers, preservatives, and/or coloring agents. General considerations in the composition and/or manufacture of pharmaceutical compositions may be found, for example, in Remington The Science and Practice of Pharmacy 21st ed., Lippincott Williams & Wilkins, 2005.

[0160] In certain embodiments, the compositions described herein can be formulated as a liquid for oral administration. Liquid compositions include solutions, suspensions and emulsions. Examples of liquid pharmaceutical preparations include propylene glycol solutions and solutions containing sweeteners for oral solutions, suspensions and emulsions. When the liquid composition comes into contact with an aqueous medium, such as for example an aqueous medium having an acidic environment, the composition forms micelles.

[0161] In certain embodiments, the dosage form comprises micelles pre-formed prior to administration to a subject in need of such administration. Such pre-formed micelles are stable at room temperature.

[0162] In other embodiments, the compositions described herein can be formulated as a fill material for a soft gelatin capsule. Likewise, when the contents of the soft gelatin capsule comes into contact with an aqueous medium, the composition forms micelles upon disintegration of the capsule.

[0163] A capsule may be prepared, e.g., by placing the compositions described above inside a capsule shell. A capsule is a dosage form administered in a special container or enclosure containing an active agent. In some embodiments the compositions described herein can be filled into soft capsules. A capsule shell may be made of methylcellulose, hydroxypropylmethyl cellulose, polyvinyl alcohols, or denatured gelatins or starch or other material. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. In some embodiments the unit dosage form is a gel capsule. In some embodiments the capsule shell is a glycerin capsule shell, for example product no. GSU0051 manufactured by SwissCaps and which meets USP 25 requirements (SwissCaps, USA 14193 SW 119th Ave., Miami/Fla., U.S. 33186). In other embodiments the capsule is a bovine gelatin shell, for example SwissCaps product no. GSU0708. Other suitable capsule shell materials include polyethylene, polypropylene, poly(methylmethacrylate), polyvinylchloride, polystyrene,

polyurethanes, polytetrafluoroethylene, nylons, polyformaldehydes, polyesters, cellulose acetate, and nitrocellulose. The capsule shell itself may contain small amounts of dyes, opaquing agents, plasticizers, and preservatives. Conventional methods for preparing other solid dosage forms, for example, capsules, suppositories, and the like are also well known. Gelatin capsule shells may be made also be made of tapioca, grass, vegetable derived or fish derived gelatin. For example K-CAPS (Capsuline, Inc. Pompano Beach, Fla.) is a certified Kosher soft capsule shell of vegetable origin. Other vegetarian derived gelatin capsules may, be made of vegetable derived hydroxypropylmethyl cellulose (HPMC). Capsules shells may also contain Modified Maize Starch, Glycerol, and Carrageenan as a gelling agent.

[0164] In other embodiments the capsule has a shell comprising the material of the rate-limiting membrane, including coating materials, and filled with the compositions described herein. Capsule shells may be made of a porous or a pH-sensitive polymer made by a thermal forming process. In certain embodiments the capsule shell in the form of an asymmetric membrane; i.e., a membrane that has a thin skin on one surface and most of whose thickness is constituted of a highly permeable porous material.

[0165] Yet another useful capsule, a "swelling plug device", can be used. The compositions described herein can be incorporated into a non-dissolving capsule-half of the device which is sealed at one end by a hydrogel plug. This hydrogel plug swells in an aqueous environment, and, after swelling for a predetermined time, exits the capsule thus opening a port through which the active agent can leave the capsule and be delivered to the aqueous environment. Preferred hydrogel-plugged capsules are those which exhibit substantially no release of active agent from the dosage form until the dosage form has exited the stomach and has resided in the small intestine for about 15 minutes or more, preferably about 30 minutes or more, thus assuring that minimal Omega-3 fatty acid ester is released in the stomach or the small intestine. Hydrogel-plugged capsules of this type have been described in patent application WO90/19168.

[0166] The dosage forms may contain a plasticizer, particularly in a capsule shell. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose, triacetin, glycerin, sorbitol, sorbitan or combinations thereof.

[0167] In additional embodiments, the compositions can be formulated as a liquid for parenteral administration.

[0168] Compositions can be formulated as one or more dosage units. In some embodiments, it can be advantageous to formulate oral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit forms described in some embodiments can refer to physically discrete units suited as unitary dosages for the

subject to be treated; each unit containing a predetermined quantity of active composition calculated to produce the desired therapeutic effect in association with the suitable pharmaceutical carrier. In certain embodiments, the dosage form may optionally contain a flavorant such as orange oil, substantially pure d-limonene, and an antioxidant such as tocopherol, ascorbyl palmitate or a combination of antioxidants.

FUNCTIONAL FOODS

[0169] In certain embodiments, the compositions described herein comprise micelles pre-formed prior to administration to a subject in need of such administration. Such pre-formed micelles are stable at room temperature.

[0170] Accordingly, either such pre-formed micelles or the pre-micellized compositions described herein can be added to foods, which can then be consumed as part of a healthy diet for enriching a subject's Omega-3 fatty acid levels or as a dietary treatment in addition to the oral/parenteral administration of the compositions described herein as prescribed by a health professional.

[0171] In certain embodiments, the functional food is in the form of edible or drinkable compositions, e.g., foodstuffs such as chewable or edible bars, confectionary products (e.g., chocolate bars), cookies, juice drinks, baked or simulated baked goods (e.g., brownies), biscuits, lozenges or chewing gum. Examples of chewable or edible bars include chocolate bars or energy bars. Such functional foods can be particularly useful to people participating in sports or other forms of exercise.

[0172] In certain embodiments, the functional foods may also be in the form of, for example, butter, margarine, bread, cake, milk shakes, ice cream, yogurt and other fermented milk product.

[0173] In certain embodiments, the functional food can also be in the form of a liquid to be sprayed on meats, salads or other foods.

[0174] Other forms of the functional foods can be breakfast cereals, such as for example, grain flakes, muesli, bran, oatmeal.

[0175] When the functional food product is in a drinkable form, the compositions described herein can be added directly to the drink, such as for example plain milk, flavored milk, fermented milk products or juices. The compositions will form micelles comprising the Omega-3 fatty acid esters in the drinkable product.

[0176] When the functional food is in the form of a solid edible product, the compositions described herein can be first added to an aqueous medium, wherein the composition will form micelles as described herein. The aqueous medium comprising the micelles can subsequently be either sprayed onto the solid edible product or mixed into the ingredients when manufacturing the edible product.

[0177] The invention is further defined by reference to the following examples, which are not meant to limit the scope of the present invention. It will be apparent to those skilled in the art that many modifications, both to the materials and methods, may be practiced without departing from the purpose and interest of the invention.

NON-LIMITING WORKING EXAMPLES

EXAMPLE 1

[0178] The amounts and percentages of the ingredients comprising the composition are shown in Table 1:

TABLE 1

COMPOSITION (FILL MASS)/dosage form		
INGREDIENT	Amount (mg)	% (wt/wt)
Total Omega-3 fatty acid Ethyl Esters	754.3	68.57
- EPA Ethyl Esters	392.2	35.65
- DHA Ethyl Esters	165.9	15.08
Polysorbate 80	337.9	30.72
Pluronic F87	7.8	0.71
GEL MASS/dosage form		
INGREDIENT	Amount (gm)	% (wt/wt)
Gelatin	270	40
Glycerin	135	20
Purified water	270	40

[0179] The manufacturing process for the dosage form comprising one embodiment of the composition can be separated into three stages: a) the process for manufacturing the composition (fill mass), b) the process for manufacturing the gel mass used for encapsulating the fill mass, and c) the encapsulation process. Stages (a) and (b) can be carried out in either order.

[0180] The process for manufacturing the composition begins by weighing appropriate amounts of the Polysorbate 80 and Pluronic F87 as per the desired batch size and mixing them to homogeneity at 60°C in a stainless steel tank. This mixture is allowed to cool to room temperature before the substantially pure Omega-3 fatty acid ethyl ester mixture is vacuum-transferred quantitatively into the same stainless steel tank containing

the Polysorbate 80 and Pluronic F87. This mixture is again mixed to homogeneity at room temperature before being blanketed with nitrogen. This final composition is also termed the "fill mass".

[0181] The process for manufacturing the gel mass begins by weighing appropriate amounts of each of the glycerin and water as per the desired batch size and mixing them to homogeneity in a separate stainless steel mixer at about 80°C. Next, the appropriate amount of gelatin is weighed as per the batch size, added to the glycerin/water mixture and again mixed to homogeneity at 80°C before being degassed under vacuum. This final mixture comprising glycerin/water/gelatin is termed the "gel mass".

[0182] Depending on the desired shape of the capsule, suitable dies and transfer tubing are installed into a soft gel encapsulation apparatus (SS-60 Softgel Encapsulation Machine by SKY Softgel Co. Ltd., Incheon, Korea). The fill mass is pumped into the dies containing a pre-formed ribbon comprising the semi-solid gel mass. The dies shape the soft gelatin capsules, which are then tumble dried for about 20 – 60 min. The capsules are transferred onto a tray and dried in a low-temperature/humidity drying room and dried until the capsules reach above 75 shore hardness. The capsules are then inspected, sorted, polished, printed and packaged into bottles. The bottles are affixed with a label, which includes prescribing information. Alternatively, the bottles can be packaged into boxes with a package insert, which includes prescribing information.

EXAMPLE 2

[0183] Experiments were conducted to determine micelle formation in two compositions, A and B, as shown in Table 2. Both compositions were prepared as described in Example 1 comprising Omega-3 fatty acid ethyl esters, in which the Omega-3 fatty acid ethyl esters had increased absorption and the food effect was substantially eliminated.

TABLE 2

Ingredients	% (wt/wt)	
	Composition A	Composition B
Omega-3 fatty acid Ethyl Esters	68.57	75.0
Polysorbate 80, NF	30.71	20.0
Pluronic F87	0.71	5.0
Combined surfactant HLB	15.3	16.8
Whole Product HLB	13	13.2

[0184] The compositions which formed well dispersed micelles generally had a combined surfactant HLB value of about 15 to about 17.

[0185] Other compositions with Polysorbate 80 levels between 27-29% in combination with Pluronic F87 between about 7% to about 22% generally formed large oil globules. These compositions had a combined surfactant HLB value of from about 17 to about 19. Based on these experiments the whole product HLB was from about 13 and about 14.4 and the combined surfactant HLB was between about 12 to about 17.

EXAMPLE 3

[0186] Compositions A and B (1,000 mg), as shown in Table 2, were added to separate containers containing 500-900 mL of water in 0.1N HCl, under United States Pharmacopeia (USP) dissolution 2 conditions, as described in General Chapter 711, United States Pharmacopeia, 34/National/2011, and observed. Neither composition was subjected to any agitation or shearing. When observed under the microscope, very small, well dispersed micelles were visible. The micelles were stable for over twelve months at room temperature and there was no apparent separation of the Omega-3 fatty acid esters from the other ingredients of the composition. Thus, compositions that included Polysorbate 80 levels between 20-31% in combination with Pluronic F87 at 0.7 to 5% formed stable micelles.

EXAMPLE 4

[0187] A human subject ingested composition A in Example 2 (the "Experimental Composition") and underwent blood monitoring to measure the increase in absorption of the Omega-3 fatty acid ethyl esters compared to the Omega-3 fatty acid ethyl esters in an Omega-3 fatty acid ethyl ester composition that is representative of currently marketed drug and nutritional Omega-3 products (the "Standard Composition"). The Standard Composition was manufactured by encapsulating Omega-3 ethyl esters using standard encapsulating methods. Absorption of Omega-3 fatty acid ethyl esters was determined by comparing changes in subject's OmegaIndex following ingestion of the compositions, as measured using the OmegaIndex test kit by OmegaQuant. Prior to ingestion of a composition, blood was drawn from the subject to determine subject's baseline OmegaIndex. The subject then ingested soft gel capsules containing either the Experimental Composition or the Standard Composition. A subsequent blood draw occurred at four hours post-ingestion. The subject remained in the fasted state from the initial baseline blood draw through the four-hour blood draw. The results are shown in Table 4.

TABLE 4

Capsule Composition	Dose	Omega Index		
	EPA+DHA Ethyl Esters	Initial	4 hour	Increase
Standard Composition	1.52 g	5.2	5.3	1.92%
Experimental Composition - Dose A (4 capsules, 400 mg total fill weight per capsule)	1.46 g	5.4	5.7	5.55%
Experimental Composition - Dose B (10 capsules, 400 mg total fill weight per capsule)	3.65 g	4.9	5.3	8.16%

EXAMPLE 5

[0188] An Open-label, Randomized, 3 arm, Parallel group, Proof of Concept Study was conducted to evaluate the serum TG lowering efficacy and safety of SC401 Capsules 1100 mg (manufactured as described in Example 1) vs. LOVAZA® (Omega-3-acid ethyl esters) Capsules 1000 mg vs. PLACEBO in hypertriglyceridemic subjects with serum TG between 250 and 500 mg/dL when dosed under fasting conditions.

[0189] The aim of this study was to evaluate the effectiveness of SC401 vs. LOVAZA® vs Placebo on TG reduction over 14 days of treatment. 45 subjects were enrolled in the study in order to complete at least 12 subjects in each of the three treatment arms.

[0190] The following inclusion and exclusion criteria were used to select the subjects for this study:

[0191] INCLUSION CRITERIA:

- Men and women 18 years of age or older;
- Serum TG between 200 and 500 mg/dL.
- Normally active and in good health on the basis of medical history, brief physical examination, electrocardiogram, and routine laboratory tests.
- Be neither over weight nor under weight for his/her height as per the attached height/weight table values (see attached height/weight table).
- Provide written informed consent.

- If female and of child bearing potential; is practicing an acceptable method of birth control for the duration of the study as judged by the investigator (s), such as condoms, foams, jellies, diaphragm, intrauterine device (IUD), or abstinence; or is postmenopausal for at least 1 year; or is surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy).

[0192] EXCLUSION CRITERIA:

- Severe hypertriglyceridemia (serum TG >500 mg/dL).
- Intolerance to Omega-3 or fish.
- Use of Omega-3 fish oil, other EPA or DHA and/or DHA fortified foods or other TG lowering medications within three months of study drug initial administration, or during the study.
- Consumption of any fish within seven days of study drug initial administration or during the study.
- Recent history of certain heart, kidney, liver, lung, or gastrointestinal diseases or cancer (except non-melanoma skin cancer).
- Diabetes or receiving insulin therapy.
- Pregnant or lactating females. Women of childbearing potential who are not using a medically approved method of contraception.
- Use of certain types of hormones, anticonvulsant drugs, immunologic drugs, antibiotic, antifungal and antiviral drugs, and cardiac drugs.
- Use of warfarin (Coumadin).
- Recent history (past 12 month) of drug abuse or alcohol abuse.
- Exposure to any investigational product, within 28 days prior to study drug administration.
- Subjects diagnosed with the following conditions:
- Endocrine diabetes mellitus, hypothyroidism, pregnancy;
- Nutritional obesity, alcohol access;
- Renal nephrotic disease, chronic renal failure;
- Hepatic disease cholestas, hepatocellular dysfunction;
- Immunoglobulin excess paraproteinemia;
- Gout;
- Any other condition the investigator believes would interfere with the patient's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the patient at undue risk; and subjects on the following

medications Thiazide diuretic, Steroid hormones, Microsomal enzyme, Retinoic acid derivatives, Protease inhibitors (HIV infection).

[0193] The Informed Consent Document (ICD) was read by the volunteer and signed prior to study specific procedures. Additionally, the following tests were be performed at clinic entry for each period

- Urine screen for drugs of abuse – including cocaine, cannabis, amphetamines, barbiturates, benzodiazepines and opiates. Subjects were rejected / withdrawn from the study if the result was positive for these drugs,
- Alcohol breath test - subjects were rejected / withdrawn from the study if the result was positive for alcohol,
- Urine pregnancy test (HCG) (for female subjects only) – Female subjects were rejected / withdrawn from the study if result was positive for pregnancy, and
- Gynecological & breast examination (for female subjects only) - subjects were rejected / withdrawn from the study if there were any abnormalities in the examination.

[0194] Subjects were housed in the clinical facility from at least 48 hours pre-dose to at least 14 days and were requested to stay for 16 consecutive nights in the facility.

[0195] Subjects were fasted for at least 10 hours before morning dosing and were instructed to abstain from consuming caffeine and /or xanthine containing products (i.e. coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.), alcohol and vitamin supplements, including vitamin C and ascorbic acid and grapefruit and its juice, for at least 48 hours prior to dosing and throughout the study. No citrus juices, including orange juice and grapefruit juice, were provided during the study.

[0196] After overnight fast of 10 hours subjects were dosed under monochromatic light or low light condition as follows:

[0197] SC401 (Omega-3 Fatty Acid Ethyl Esters, 1100 mg) 2 capsules (as single dose), taken upon awakening (at least 2 hours before breakfast taken with water only on an empty stomach); then 2 capsules (as single dose) taken at bedtime (at least 2 hours after dinner taken with water only and no food or liquids thereafter for the night), or

[0198] LOVAZA® (Omega-3 Fatty Acid Ethyl Esters, 1000 mg, of GlaxoSmithKline, RTP, NC 2770) 2 capsules (as single dose) taken upon awakening (at least 2 hour before breakfast taken with water only on an empty stomach); then 2

capsules (as single dose) taken at bedtime (at least 2 hours after dinner taken with water only and no food or liquids thereafter for the night), or

[0199] PLACEBO (Ethyl Oleate, 1000 mg capsules) 2 capsules (as single dose) taken upon awakening (at least 2 hour before breakfast taken with water only on an empty stomach); then 2 capsules (as single dose) taken at bedtime (at least 2 hours after dinner taken with water only and no food or liquids thereafter for the night).

[0200] The amounts of Omega-3 fatty acid ethyl esters comprising Lovaza, SC401 and the placebo are shown in the Table 5 below:

TABLE 5

Capsule Fill Composition (mg)	SC401	Lovaza®	Placebo
Total Omega-3 Fatty Acid Ethyl Esters	754.3	934	0
- EPA Ethyl Esters	392.2	482	0
- DHA Ethyl Esters	165.9	370	0
Polysorbate 80, NF	337.9	0	0
Pluronic F87	7.8	0	0
Ethyl Oleate	0	0	1000

[0201] 4 blood samples (8 mL each) were collected over the study period. The blood samples will be collected at T_s, T_0, T_{7d}, T_{14d} in plain vacuum tubes by direct vein puncture. Vacutainers were placed upright in a rack kept in wet ice bath until transferred to Diagnostic department.

[0202] For T_s, T_0, T_{7d}, T_{14d}, fasting triglyceride/HDL/LDL/total cholesterol/non-HDL/ levels for each patient in each of three groups was determined.

[0203] The data are tabulated in Table 6 below:

TABLE 6

	Results at Day 14 from Baseline*		
	SC401	Lovaza®	Placebo
Serum blood levels of triglycerides	-48.5%	-29.4%	-27.7%
*SC401 results adjusted to match amount of total EPA and DHA ethyl esters dosed in Lovaza® arm.			

CLAIM SET A

1. A pharmaceutical composition comprising at least one Omega-3 fatty acid ester and at least one surface active agent; wherein said at least one Omega-3 fatty acid ester comprises at least about 40% (wt/wt) of the composition, and wherein said composition is free of Omega-3 free fatty acids.

2. The composition of claim 1 wherein said at least one Omega-3 fatty acid ester is selected from the group consisting of hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentenoic acid, docosahexaenoic acid, tetracosapentenoic acid, tetracosahexaenoic acid, or combinations thereof.

3. The composition of claim 1 wherein said at least one Omega-3 fatty acid ester is substantially pure.

4. The composition of claim 1 wherein said at least one Omega-3 fatty acid ester is an ethyl ester.

5. The composition of claim 4 wherein said at least one ethyl ester comprises a mixture of EPA and DHA ethyl esters, wherein the ratio of EPA:DHA is more than 2:1 to not more than 3.4:1 and wherein said EPA and DHA ethyl esters combined comprise from about 40% (wt/wt) to about 85% (wt/wt) of said composition.

6. The composition of claim 3 wherein the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

7. The composition of claim 3 wherein said at least one ethyl ester comprises a mixture of EPA and DHA ethyl esters, wherein the ratio of EPA:DHA is about 2.4:1 and wherein said EPA and DHA ethyl esters combined comprise from about 40% (wt/wt) to about 85% (wt/wt) of said composition.

8. The composition of claim 7 wherein the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

9. The composition of claim 1 wherein said at least one surface active agent has hydrophilic-lipophilic balance of at least 8.0.

10. The composition of claim 1 wherein said at least one surface active agent is selected from the group consisting of any of at least one anionic surface active agent, at least one non-ionic surface active agent, at least one zwitterionic surface active agent, at least one cationic surface active agent, or combinations thereof.

11. The composition of claim 1 wherein said at least one surface active agent comprises at least one non-ionic surface active agent selected from the group consisting of any of at least one polysorbate, at least one poloxamer, or combinations thereof.

12. The composition of claim 1 wherein said at least one surface active agent comprises at least one polysorbate from about 15% wt/wt to about 31% wt/wt of said composition.

13. The composition of claim 1 wherein said at least one surface active agent is Polysorbate 80.

14. The composition of claim 1 wherein said at least one surface active agent comprises at least one poloxamer from about 0.5% wt/wt to about 5% wt/wt of said composition.

15. The composition of claim 1 further comprising at least one antioxidant.

16. The composition of claim 1 further comprising at least one antioxidant selected from the group consisting of any of at least one tocopherol, at least one tocotrienol, or a combination thereof.

17. The composition of claim 1 further comprising at least one tocopherol.

18. The composition of claim 1 further comprising from about 0.01% (wt/wt) to about 5% (wt/wt) of said composition at least one tocopherol.

19. The composition of claim 1 further comprising at least one terpene.

20. The composition of claim 1 further comprising substantially pure d-limonene.

21. The composition of claim 1 further comprising from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition substantially pure d-limonene.

22. The composition of claim 1 further comprising from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition natural orange oil.

23. The composition of claim 1 wherein said composition forms micelles in an aqueous medium.

24. The composition of claim 1 wherein said composition forms micelles in an aqueous medium having an acidic pH.

25. The composition of claim 1 wherein said composition forms micelles in 0.1N HCl.

26. The composition of claim 24 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

27. The composition of claim 25 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

28. The composition of claim 26 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

29. The composition of claim 1 wherein said composition is administered to a human subject in need of such administration with or without food.

30. The composition of claim 1 wherein said at least one Omega-3 fatty acid ester consists essentially of an ethyl ester.

31. The composition of claim 21 wherein said composition when administered to a human subject having serum TG levels of ≥ about 155 mg per dL blood serum, lowers said subject's TG levels by at least about 20 %.

32. A mixed Omega-3 fatty acid ester pharmaceutical composition comprising of EPA and DHA ethyl esters in a ratio of more than 2:1 to not more than 3.4:1, from about 15% to about 31% Polysorbate 80 and from about 0.5% (wt/wt) to about 5% (wt/wt) Pluronic F87; wherein Omega-3 fatty acid esters comprise at least about 50% (wt/wt) of the composition and wherein said composition is free of Omega-3 free fatty acids.

33. The composition of claim 32 further comprising at least one antioxidant selected from the group consisting of any of at least one tocopherol, at least one tocotrienol, or a combination thereof.

34. The composition of claim 32 further comprising at least one tocopherol.

35. The composition of claim 32 further comprising from about 0.01% (wt/wt) to about 5% (wt/wt) of said composition at least one tocopherol.

36. The composition of claim 32 further comprising at least one terpene.

37. The composition of claim 32 further comprising substantially pure d-limonene.

38. The composition of claim 32 further comprising from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition substantially pure d-limonene.

39. The composition of claim 32 further comprising from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition natural orange oil.

40. The composition of claim 32 wherein said composition forms micelles in an aqueous medium.

41. The composition of claim 32 wherein said composition forms micelles in an aqueous medium having an acidic pH.

42. The composition of claim 32 wherein said composition forms micelles in 0.1N HCl.

43. The composition of claim 40 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

44. The composition of claim 41 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

45. The composition of claim 42 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

46. The composition of claim 38 wherein said composition when administered to a human subject having serum TG levels of ≥ 155 mg TG per dL serum, lowers said subject's TG levels by at least about 20 %.

47. The composition of claim 32 wherein said composition when administered to a human subject is substantially independent of food effect.

48. The composition of claim 32 consisting essentially of EPA and DHA ethyl esters.

49. A method of treating a cardiovascular condition or disorder in a subject in need of such treatment, said method comprising administering to said subject a therapeutically effective amount of a composition comprising at least one Omega-3 fatty acid ester and least one surface active agent; wherein said at least one Omega-3 fatty acid ester comprises at least about 40% (wt/wt) of said composition and wherein said composition is free of Omega-3 free fatty acids.

50. The method of claim 49 wherein said at least one Omega-3 fatty acid ester is selected from the group consisting of hexadecatrienoic acid, α-linolenic acid, stearidonic acid, eicosatrienoic acid, eicosapentaenoic acid, heneicosapentaenoic acid, docosapentenoic acid, docosahexaenoic acid, tetracosapentenoic acid, tetracosahexaenoic acid, or combinations thereof.

51. The method of claim 49 wherein said at least one Omega-3 fatty acid ester is an ethyl ester.

52. The method of claim 49 wherein said at least one ethyl ester comprises a mixture of EPA and DHA ethyl esters, wherein the ratio of EPA:DHA is more than 2:1 to not more than 3.4:1 and wherein said EPA and DHA ethyl esters combined comprise from about 40% (wt/wt) to about 85% (wt/wt) of said composition.

53. The method of claim 49 wherein the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

54. The method of claim 49 wherein said at least one Omega-3 fatty acid ethyl ester comprises a mixture of EPA and DHA ethyl esters, wherein the ratio of EPA:DHA is about 2.4:1 and wherein said EPA and DHA ethyl ester combined comprise from about 40% (wt/wt) to about 85% (wt/wt) of said composition.

55. The method of claim 54 wherein the EPA and DHA ethyl esters combined comprise about 50% (wt/wt) of said composition.

56. The method of claim 49 wherein said at least one surface active agent has hydrophilic-lipophilic balance of at least 8.0.

57. The method of claim 49 wherein said at least one surface active agent is selected from the group consisting of at least one anionic surface active agent, at least one non-ionic surface active agent, at least one zwitterionic surface active agent, at least one cationic surface active agent, or combinations thereof

58. The method of claim 49 wherein said least one surface active agent comprises at least one non-ionic surface active agent selected from the group consisting of at least one polysorbate, at least one poloxamer, or combinations thereof.

59. The method of claim 49 wherein said at least one surface active agent comprises at least one polysorbate from about 15% wt/wt to about 31% wt/wt of said composition.

60. The method of claim 49 herein said at least one surface active agent is Polysorbate 80.

61. The method of claim 49 wherein said at least one surface active agent comprises from about 0.5% wt/wt to about 5% wt/wt of said composition at least one poloxamer.

62. The method of claim 49 further comprising at least one antioxidant.

63. The method of claim 49 further comprising at least one antioxidant selected from the group consisting of at least one tocopherol, at least one tocotrienol, and a combination thereof.

64. The method of claim 49 further comprising at least one tocopherol.

65. The method of claim 49 further comprising from about 0.01% (wt/wt) to about 5% (wt/wt) of said composition at least one tocopherol.

66. The method of claim 49 further comprising at least one terpene.

67. The method of claim 49 further comprising substantially pure d-limonene.

68. The method of claim 49 further comprising from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition substantially pure d-limonene.

69. The method of claim 49 further comprising from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition natural orange oil.

70. The method of claim 49 wherein said composition forms micelles in an aqueous medium.

71. The method of claim 49 wherein said composition forms micelles in an aqueous medium having an acidic pH.

72. The method of claim 49 wherein said composition forms micelles in 0.1N HCl

73. The method of claim 70 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

74. The method of claim 71 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

75. The method of claim 72 wherein said micelles have a diameter of from about 1 μm to about 10 μm.

76. The method of claim 47 wherein said composition is administered to a human subject with our without food.

77. The method of claim 49 wherein said at least one Omega-3 fatty acid ester consists essentially of at least one ethyl ester.

78. The method of claim 49 wherein said cardiovascular condition or disorder is selected from the group consisting of disorders of the heart and vasculature, including, for example, hypertension, hyperlipidemia, hypertriglyceridemia, atherosclerosis, transient ischemic attack, systolic dysfunction, diastolic dysfunction, aneurysm, aortic dissection, myocardial ischemia, acute myocardial infarction (AMI), acute ST-segment elevation myocardial infarction (STEMI), acute non-ST -segment elevation myocardial infarction (NSTEMI), angina pectoris, unstable angina (UA), and stable angina (SA), myocardial infarction, congestive heart failure, dilated congestive cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, corpulmonale, arrhythmia,

valvular heart disease, endocarditis, pulmonary embolism, venous thrombosis, peripheral vascular disease, and peripheral artery disease.

79. The composition of claim 49 wherein said cardiovascular condition or disorder is selected from the group consisting of hypertension, hyperlipidemia, and a combination thereof.

80. The composition of claim 49 wherein said cardiovascular condition or disorder is selected from the group consisting of hypertension, hyperlipidemia, and a combination thereof.

81. The composition of claim 49 wherein said cardiovascular condition or disorder is hypertriglyceridemia.

82. The method of claim 81 wherein the total amount of serum triglyceride(s) is reduced by at least 20% within about 30 days of administration of said composition to a human subject.

83. The method of claim 82 wherein the total concentration of serum low-density lipoprotein (LDL) in said human subject's blood does not substantially increase within thirty days of administration of said composition.

84. The method of claim 54 wherein said therapeutically effective amount of the composition comprises at least 0.5g/day.

85. The method of claim 54 wherein said subject's blood serum has a concentration of at least about 20 nmol/mL of the Omega-3 fatty acid ester within about four hours after administration.

86. The method of claim 49 wherein said composition is administered to a subject orally.

87. The method of claim 49 wherein said composition is administered to a subject as a gel or liquid capsule.

88. The method of claim 49 wherein said composition is administered as a parenteral composition.

89. The method of claim 49 wherein said composition is administered in combination with a non-Omega-3 fatty acid ester lipid-lowering agent to a human subject.

90. The method of claim 89 wherein said non-Omega-3 fatty acid ester lipid-lowering agent is selected from the group consisting of cholesterol absorption inhibitors, bile acid sequestrants/resins, statins, niacin and derivatives, MTP inhibitors, fibrates and CETP inhibitors.

91. The method of claim 49 wherein said composition when administered to a human subject having serum TG levels of ≥ 155 mg TG per dL serum lowers said subject's TG levels by at least about 20%.

92. A kit comprising the composition of claim 1 in a package together with instructions for using said composition to treat a cardiovascular condition or disorder.

93. The kit of claim 92 wherein said composition is in a dosage form of a gel or liquid capsule packaged in a blister package or in bottles.

94. The kit of claim 92 wherein said instructions include administering said composition with or without food.

95. The kit of claim 92 wherein said instructions include administering said composition to a human subject having serum TG levels of ≥ 150 mg TG per dL with or without food.

96. A kit comprising the composition of claim 32 in a package together with instructions for using the composition to treat a cardiovascular condition or disorder.

97. The kit of claim 96 wherein said composition is in a dosage form of a gel or liquid capsule packaged in a blister package or in bottles.

98. The kit of claim 96 wherein said instructions include administering said composition with or without food.

99. The kit of claim 96 wherein said instructions include administering said composition to a human subject having serum TG levels of ≥ 150 mg TG per dL with or without food.

100. A functional food comprising an edible solid and a pharmaceutical composition comprising at least one Omega-3 fatty acid ester and at least one surface active agent; wherein said at least one Omega-3 fatty acid ester comprises at least about 40% (wt/wt) of the composition and wherein said composition is substantially free of Omega-3 free fatty acids.

101. A functional food comprising an edible liquid and a pharmaceutical composition comprising at least one Omega-3 fatty acid ester and at least one surface active agent; wherein said at least one Omega-3 fatty acid ester comprises at least about 40% (wt/wt) of the composition and wherein said composition is substantially free of Omega-3 free fatty acids.

102. A functional food comprising an edible solid and a pharmaceutical composition comprising EPA and DHA ethyl esters in a ratio of more than 2:1 to not more than 3.4:1, from about 15% (wt/wt) to about 31% (wt/wt) Polysorbate 80, and from about 0.5% (wt/wt) to about 5% (wt/wt) Pluronic F87; wherein said EPA and DHA ethyl esters comprise at least about 40% (wt/wt) of the composition and said composition is substantially free of Omega-3 free fatty acids.

103. A functional food comprising an edible liquid and a pharmaceutical composition comprising EPA and DHA ethyl esters in a ratio of more than 2:1 to not more than 3.4:1, from about 15% (wt/wt) to about 31% (wt/wt) Polysorbate 80, and from about 0.5% (wt/wt) to about 5% (wt/wt) Pluronic F87; wherein said EPA and DHA ethyl esters comprise at least about 40% (wt/wt) of the composition and wherein said composition is free of Omega-3 free fatty acids.

104. A method of treating a human subject at risk of or suffering from cardiovascular disease comprising administering an effective amount of a functional food according to claim 100.

105. A method of treating a human subject at risk of or suffering from cardiovascular disease comprising administering an effective amount of a functional food according to claim 101.

106. A method of treating a human subject at risk of or suffering from cardiovascular disease comprising administering an effective amount of a functional food according to claim 102.

107. A method of treating a human subject at risk of or suffering from cardiovascular disease comprising administering an effective amount of a functional food according to claim 103.

108. A pharmaceutical composition comprising at least one EPA ester and at least one DHA ester in a weight to weight ratio of more than 2:1 to not more than 3.4:1 (EPA:DHA), wherein said at least one EPA ester and said at least one DHA ester combined comprises from about 40% to about 95% by weight of said composition and wherein said composition is free of active ingredients other than Omega-3 fatty acid esters.

109. The method of claim 108 wherein the composition further comprises at least one terpene.

110. The composition of claim 108 wherein the composition further comprises substantially pure d-limonene from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition.

111. A method of treating a cardiovascular condition or disorder in a subject in need of such treatment, said method comprising administering to said subject a therapeutically effective amount of a composition comprising at least one EPA ester and at least one DHA ester thereof in a weight to weight ratio of more than 2:1 to not more than 3.4:1 (EPA:DHA), wherein said at least one EPA ester and at least one DHA ester combined comprises from about 40% to about 95% by weight of the composition and wherein said composition is substantially free of active ingredients other than Omega-3 fatty acid esters.

112. The method of claim 111 wherein said composition further comprises at least one terpene.

113. The method of claim 111 wherein said composition further comprises substantially pure d-limonene from about 0.1% (wt/wt) to about 5% (wt/wt) of said composition.

114. A pharmaceutical composition comprising at least one Omega-3 fatty acid ester and at least one terpene; wherein said at least one Omega-3 fatty acid ester comprises at least about 40% (wt/wt) of the composition and is substantially free of active ingredients other than said at least one Omega-3 fatty acid ester.

115. The composition of claim 114 wherein the at least one terpene is d-limonene.

116. The composition of claim 114 wherein the at least one terpene is substantially pure d-limonene.

117. The composition of claim 114 wherein the at least one terpene is at least 95% pure d-limonene.

118. A composition comprising a mixture of EPA and DHA ethyl esters and at least one terpene, wherein the ratio of EPA:DHA is about 2.4:1 and wherein said EPA and DHA ethyl esters combined comprise from about 40% (wt/wt) to about 95% (wt/wt) of said composition and is free of active ingredients other than said EPA and DHA esters and at least one terpene.

119. The composition of claim 118 wherein the at least one terpene is d-limonene.

120. The composition of claim 118 wherein the at least one terpene is substantially pure d-limonene.

121. The pharmaceutical composition of claim 118 wherein the at least one terpene is at least 95% pure d-limonene.

FIGURE 1

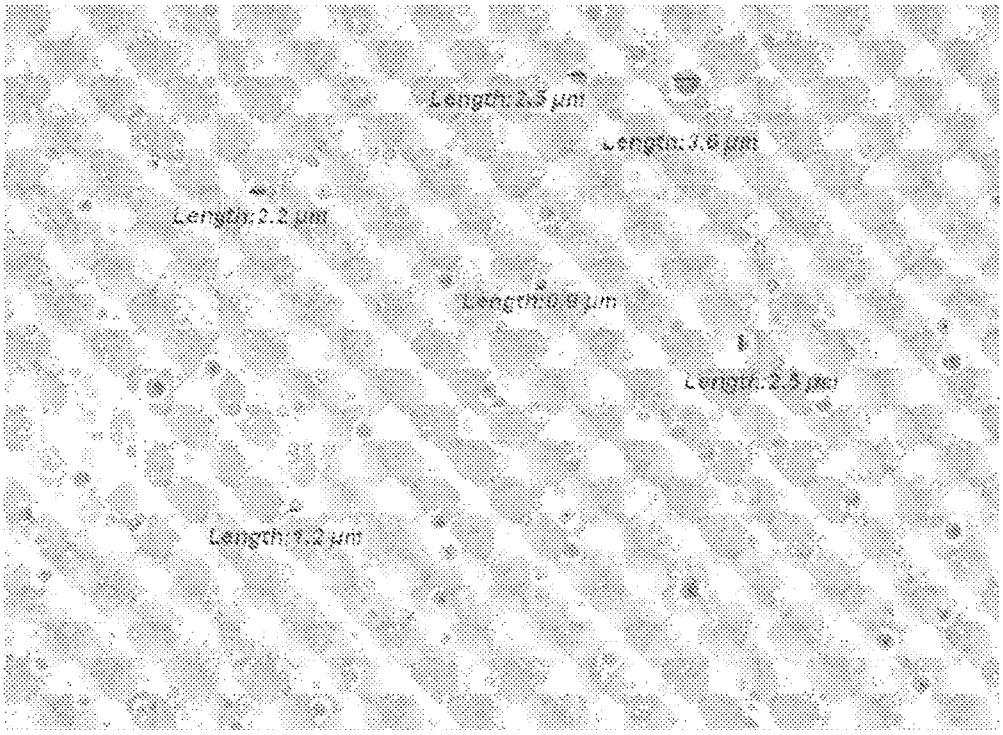


FIGURE 2

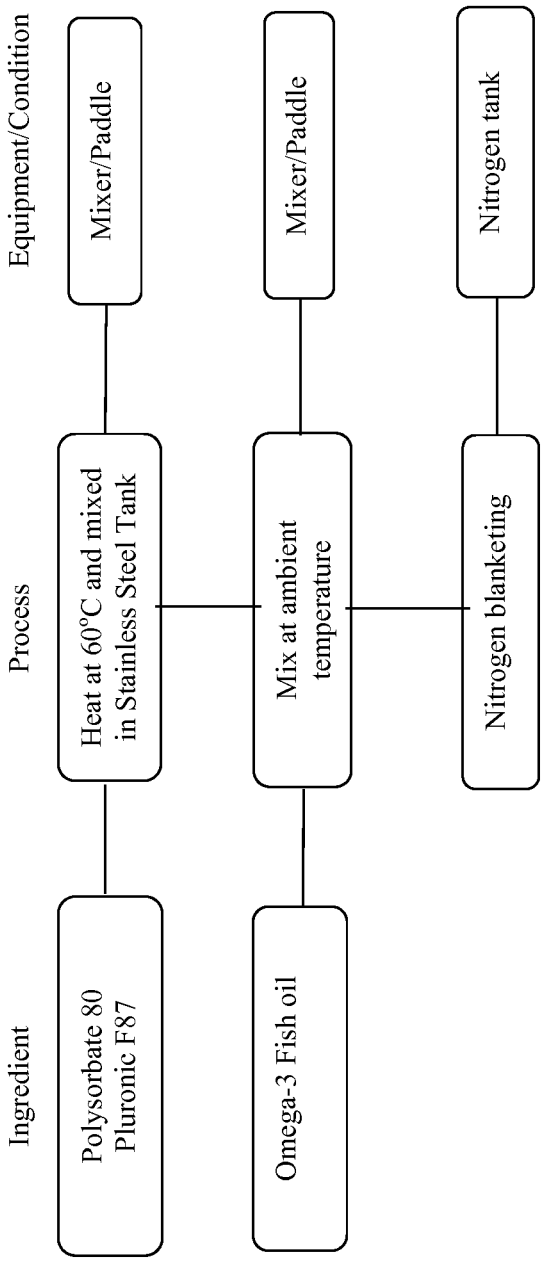

Ingredient
Process
Equipment/Condition
Polysorbate 80
Pluronic F87
Heat at 60°C and mixed in Stainless Steel Tank
Mixer/Paddle
Omega-3 Fish oil
Mix at ambient temperature
Mixer/Paddle
Nitrogen blanketing
Nitrogen tank

FIGURE 3

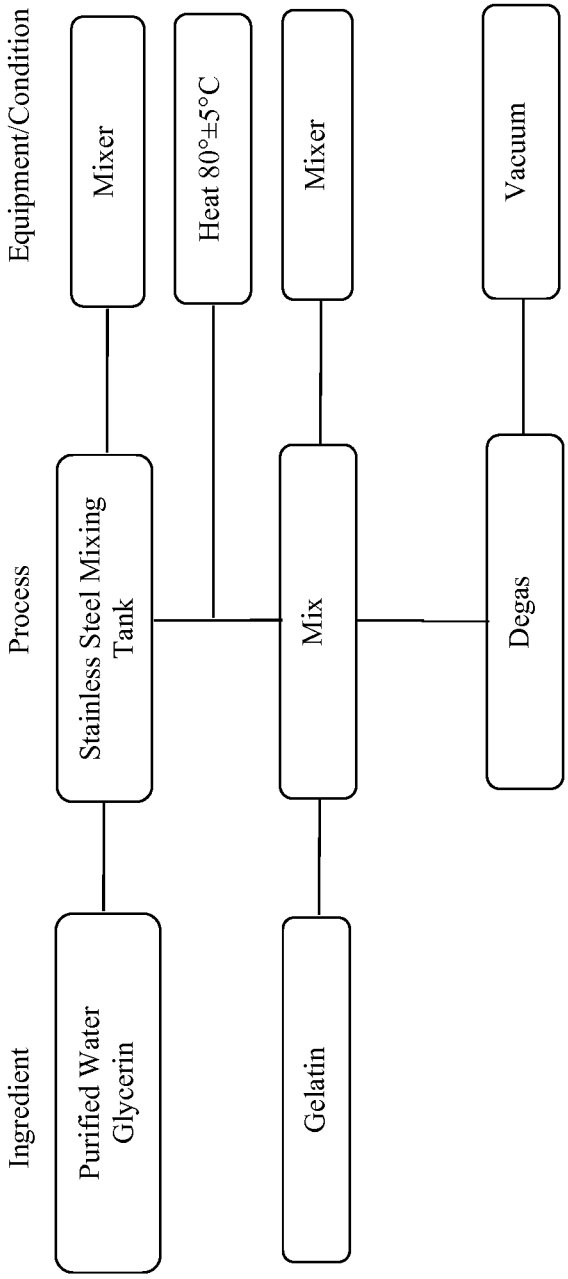
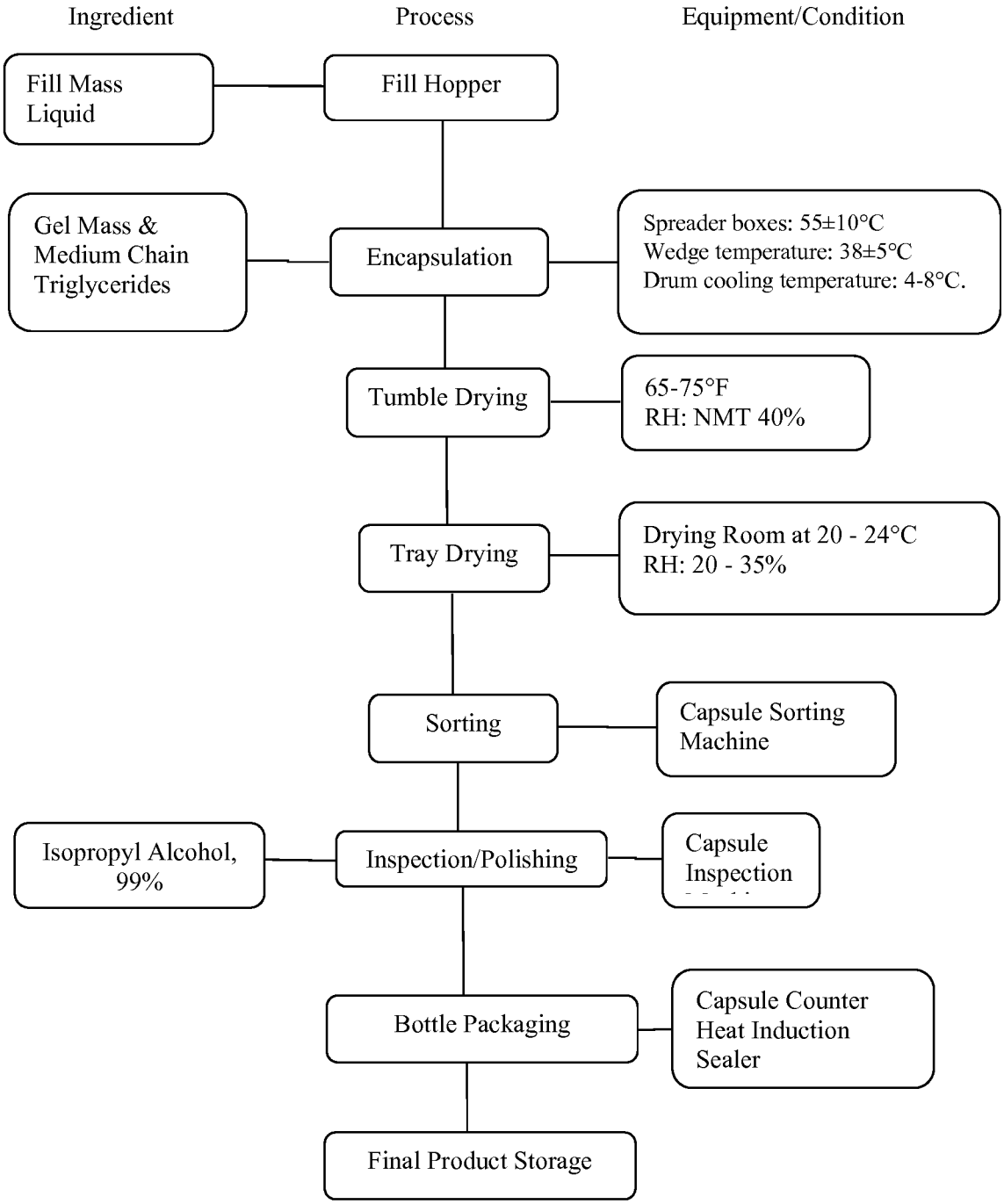

Ingredient
Process
Equipment/Condition
Purified Water
Glycerin
Stainless Steel Mixing Tank
Mixer
Heat 80°±5°C
Gelatin
Mix
Mixer
Degas
Vacuum

FIGURE 4


Ingredient
Process
Equipment/Condition
Fill Mass Liquid
Fill Hopper
Gel Mass & Medium Chain Triglycerides
Encapsulation
Spreader boxes: 55±10°C
Wedge temperature: 38±5°C
Drum cooling temperature: 4-8°C.
Tumble Drying
65-75°F
RH: NMT 40%
Tray Drying
Drying Room at 20 - 24°C
RH: 20 - 35%
Sorting
Capsule Sorting Machine
Isopropyl Alcohol, 99%
Inspection/Polishing
Capsule Inspection
Bottle Packaging
Capsule Counter Heat Induction Sealer
Final Product Storage

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/030211

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61K31/232 A61K31/7024 A61P9/00 A61P9/14
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 782 807 A1 (MOCHIDA PHARM CO LTD [JP]) 9 May 2007 (2007-05-09) the whole document	1-121
X	EP 1 946 755 A1 (MOCHIDA PHARM CO LTD [JP]) 23 July 2008 (2008-07-23) the whole document	1-121
X	EP 2 433 630 A1 (MOCHIDA PHARM CO LTD [JP]) 28 March 2012 (2012-03-28) the whole document paragraphs [0018], [0043], [0050], [0061], [0062], [0064]; claims 1,6,13	1-18, 23-35, 40-65, 70-108, 111

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
26 April 2013	07/05/2013

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/030211

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 2012/032414 A2 (PRONOVA BIOPHARMA NORGE AS [NO]; HUSTVEDT SVEIN OLAF [NO]; OLESEN PREB) 15 March 2012 (2012-03-15) the whole document examples 3-5	1-18, 23-35, 40-65, 70-108, 111
X	WO 00/48592 A1 (PHARMACIA & UPJOHN SPA [IT]; PAMPARANA FRANCO [IT]) 24 August 2000 (2000-08-24) the whole document	1-10, 15-18, 29-31, 49-57, 62-65, 76-78, 84-101, 104,105, 107,108, 111
X	WO 99/29316 A1 (SEVERSON MARY L [US]; CYCLOSPORINE THERAPEUTICS LIMI [IE]; MISHRA AWAD) 17 June 1999 (1999-06-17) the whole document page 14; example 5; tables 1,4,5 formulations 6-8; page 33, paragraph 4; table 14	1-48, 92-99, 114-121
A	WO 2011/048493 A1 (PRONOVA BIOPHARMA NORGE AS [NO]; KLAVENESS JO ERIK JOHNSRUD [NO]; BERG) 28 April 2011 (2011-04-28) the whole document	1-121
A	WO 2012/032417 A2 (PRONOVA BIOPHARMA NORGE AS [NO]; HUSTVEDT SVEIN OLAF [NO]; BERGE GUNNA) 15 March 2012 (2012-03-15) the whole document	1-121

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International application No
PCT/US2013/030211

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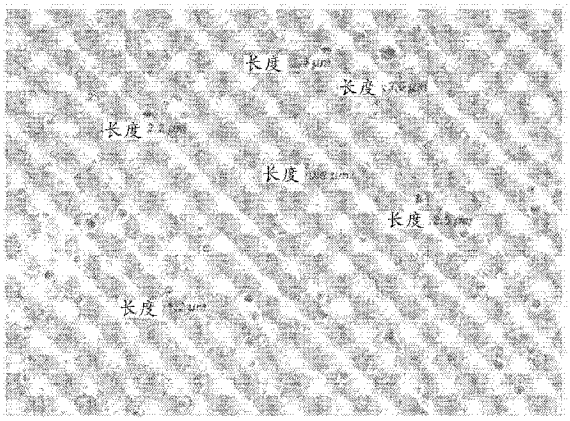
权利要求书7页 说明书34页 附图3页

(54)发明名称

ω-3脂肪酸酯组合物

(57)摘要

在此描述的是包含至少一种ω-3脂肪酸酯和至少一种表面活性剂的组合物；其中这些组合物在与一种水性介质接触时形成胶束。还提供了向受试者给予包含至少一种ω-3脂肪酸酯和至少一种表面活性剂的组合物的方法，其中该至少一种ω-3脂肪酸酯在与一种水性介质接触时形成胶束，并且该至少一种ω-3脂肪酸酯的生物利用度基本上不受食物效应的影响。所述组合物对于治疗受试者中的心血管病症或失调以及对于减少与摄入ω-3脂肪酸酯相关联的副作用是有用的。还描述了用于给予所述组合物的不同剂型以及所述组合物在功能食品中的用途。在此还提供了带有关于怎样给予所述组合物的说明书的药盒。



CN 104321053 A

1. 一种包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂的药用组合物；其中所述至少一种 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物，并且其中所述组合物不含 ω-3 游离脂肪酸。

2. 如权利要求 1 所述的组合物，其中所述至少一种 ω-3 脂肪酸酯选自下组，该组的组成为：十六碳三烯酸、α - 亚麻酸、十八碳四烯酸、二十碳三烯酸、二十碳五烯酸、二十一碳五烯酸、二十二碳五烯酸、二十二碳六烯酸、二十四碳五烯酸、二十四碳六烯酸、或它们的组合。

3. 如权利要求 1 所述的组合物，其中所述至少一种 ω-3 脂肪酸酯是基本上纯的。

4. 如权利要求 1 所述的组合物，其中所述至少一种 ω-3 脂肪酸酯是一种乙酯。

5. 如权利要求 4 所述的组合物，其中所述至少一种乙酯包括 EPA 乙酯和 DHA 乙酯的混合物，其中 EPA:DHA 的比率为大于 2:1 到不大于 3.4:1，其中所述组合的 EPA 乙酯和 DHA 乙酯构成从大约 40％ (wt/wt) 到大约 85％ (wt/wt) 的所述组合物。

6. 如权利要求 3 所述的组合物，其中这种组合的 EPA 乙酯和 DHA 乙酯构成大约 50％ (wt/wt) 的所述组合物。

7. 如权利要求 3 所述的组合物，其中所述至少一种乙酯包括 EPA 乙酯和 DHA 乙酯的混合物，其中 EPA:DHA 的比率为大约 2.4:1，并且其中所述组合的 EPA 乙酯和 DHA 乙酯构成从大约 40％ (wt/wt) 到大约 85％ (wt/wt) 的所述组合物。

8. 如权利要求 7 所述的组合物，其中这种组合的 EPA 乙酯和 DHA 乙酯构成大约 50％ (wt/wt) 的所述组合物。

9. 如权利要求 1 所述的组合物，其中所述至少一种表面活性剂具有至少 8.0 的亲水 - 亲油平衡值。

10. 如权利要求 1 所述的组合物，其中所述至少一种表面活性剂选自下组，该组的组成为：至少一种阴离子表面活性剂、至少一种非离子型表面活性剂、至少一种两性离子表面活性剂、至少一种阳离子表面活性剂中的任何一种，或它们的组合。

11. 如权利要求 1 所述的组合物，其中所述至少一种表面活性剂包括选自下组的至少一种非离子型表面活性剂，该组的组成为：至少一种聚山梨酯、至少一种泊洛沙姆中的任何一种，或它们的组合。

12. 如权利要求 1 所述的组合物，其中所述至少一种表面活性剂包括所述组合物的从大约 15％ wt/wt 到大约 31％ wt/wt 的至少一种聚山梨酯。

13. 如权利要求 1 所述的组合物，其中所述至少一种表面活性剂是聚山梨酯 80。

14. 如权利要求 1 所述的组合物，其中所述至少一种表面活性剂包括所述组合物的从大约 0.5％ wt/wt 到大约 5％ wt/wt 的至少一种泊洛沙姆。

15. 如权利要求 1 所述的组合物，进一步包含至少一种抗氧化剂。

16. 如权利要求 1 所述的组合物，进一步包含选自下组的至少一种抗氧化剂，该组的组成为：至少一种生育酚、至少一种生育三烯酚中的任何一种，或它们的组合。

17. 如权利要求 1 所述的组合物，进一步包含至少一种生育酚。

18. 如权利要求 1 所述的组合物，进一步包含所述组合物的从大约 0.01％ (wt/wt) 到大约 5％ (wt/wt) 的至少一种生育酚。

19. 如权利要求 1 所述的组合物，进一步包含至少一种萜。

20. 如权利要求 1 所述的组合物，进一步包含基本上纯的 d- 柠檬烯。

21. 如权利要求 1 所述的组合物，进一步包含所述组合物的从大约 0.1％ (wt/wt) 到大约 5％ (wt/wt) 的基本上纯的 d- 柠檬烯。

22. 如权利要求 1 所述的组合物，进一步包含所述组合物的从大约 0.1％ (wt/wt) 到大约 5％ (wt/wt) 的天然橙油。

23. 如权利要求 1 所述的组合物，其中所述组合物在一种水性介质中形成胶束。

24. 如权利要求 1 所述的组合物，其中所述组合物在一种具有酸性 pH 的水性介质中形成胶束。

25. 如权利要求 1 所述的组合物，其中所述组合物在 0.1N HCl 中形成胶束。

26. 如权利要求 24 所述的组合物，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

27. 如权利要求 25 所述的组合物，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

28. 如权利要求 26 所述的组合物，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

29. 如权利要求 1 所述的组合物，其中所述组合物与食物一起或不与食物一起给予至需要这样的给予的人类受试者。

30. 如权利要求 1 所述的组合物，其中所述至少一种 ω-3 脂肪酸酯主要由一种乙酯组成。

31. 如权利要求 21 所述的组合物，其中所述组合物在给予至具有≥大约 155mg/dL 血清的血清 TG 水平的人类受试者时降低了所述受试者的 TG 水平的至少大约 20％。

32. 一种混合 ω-3 脂肪酸酯药用组合物，其包含处于大于 2:1 到不大于 3.4:1 比率的 EPA 乙酯和 DHA 乙酯、从大约 15％到大约 31％的聚山梨酯 80 以及从大约 0.5％ (wt/wt) 到大约 5％ (wt/wt) 的普朗尼克 F87 ；其中 ω-3 脂肪酸酯构成至少大约 50％ (wt/wt) 的该组合物，并且其中所述组合物不含 ω-3 游离脂肪酸。

33. 如权利要求 32 所述的组合物，进一步包含选自下组的至少一种抗氧化剂，该组的组成为 ：至少一种生育酚、至少一种生育三烯酚中的任何一种，或它们的组合。

34. 如权利要求 32 所述的组合物，进一步包含至少一种生育酚。

35. 如权利要求 32 所述的组合物，进一步包含所述组合物的从大约 0.01％ (wt/wt) 到大约 5％ (wt/wt) 的至少一种生育酚。

36. 如权利要求 32 所述的组合物，进一步包含至少一种萜。

37. 如权利要求 32 所述的组合物，进一步包含基本上纯的 d- 柠檬烯。

38. 如权利要求 32 所述的组合物，进一步包含所述组合物的从大约 0.1％ (wt/wt) 到大约 5％ (wt/wt) 的基本上纯的 d- 柠檬烯。

39. 如权利要求 32 所述的组合物，进一步包含所述组合物的从大约 0.1％ (wt/wt) 到大约 5％ (wt/wt) 的天然橙油。

40. 如权利要求 32 所述的组合物，其中所述组合物在一种水性介质中形成胶束。

41. 如权利要求 32 所述的组合物，其中所述组合物在一种具有酸性 pH 的水性介质中形成胶束。

42. 如权利要求 32 所述的组合物，其中所述组合物在 0.1N HCl 中形成胶束。

43. 如权利要求 40 所述的组合物，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

44. 如权利要求 41 所述的组合物，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

45. 如权利要求 42 所述的组合物，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

46. 如权利要求 38 所述的组合物，其中所述组合物在给予至具有≥ 155mg TG/dL 血清的血清 TG 水平的人类受试者时降低了所述受试者的 TG 水平的至少大约 20%。

47. 如权利要求 32 所述的组合物，其中所述组合物在给予至人类受试者时基本上不受食物效应的影响。

48. 如权利要求 32 所述的组合物，主要由 EPA 乙酯和 DHA 乙酯组成。

49. 一种治疗需要这样的治疗的受试者中的心血管病症或失调的方法，所述方法包括向所述受试者给予治疗有效量的包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂的组合物；其中所述至少一种 ω-3 脂肪酸酯构成至少大约 40% (wt/wt) 的所述组合物，并且其中所述组合物不含 ω-3 游离脂肪酸。

50. 如权利要求 49 所述的方法，其中所述至少一种 ω-3 脂肪酸酯选自下组，该组的组成为：十六碳三烯酸、α-亚麻酸、十八碳四烯酸、二十碳三烯酸、二十碳五烯酸、二十一碳五烯酸、二十二碳五烯酸、二十二碳六烯酸、二十四碳五烯酸、二十四碳六烯酸，或它们的组合。

51. 如权利要求 49 所述的方法，其中所述至少一种 ω-3 脂肪酸酯是一种乙酯。

52. 如权利要求 49 所述的方法，其中所述至少一种乙酯包括 EPA 乙酯和 DHA 乙酯的混合物，其中 EPA:DHA 的比率为大于 2:1 到不大于 3.4:1，其中所述组合的 EPA 乙酯和 DHA 乙酯构成从大约 40% (wt/wt) 到大约 85% (wt/wt) 的所述组合物。

53. 如权利要求 49 所述的方法，其中这种组合的 EPA 乙酯和 DHA 乙酯构成大约 50% (wt/wt) 的所述组合物。

54. 如权利要求 49 所述的方法，其中所述至少一种 ω-3 脂肪酸乙酯包括 EPA 乙酯和 DHA 乙酯的混合物，其中 EPA:DHA 的比率为大约 2.4:1，其中所述组合的 EPA 乙酯和 DHA 乙酯构成从大约 40% (wt/wt) 到大约 85% (wt/wt) 的所述组合物。

55. 如权利要求 54 所述的方法，其中该组合的 EPA 乙酯和 DHA 乙酯构成大约 50% (wt/wt) 的所述组合物。

56. 如权利要求 49 所述的方法，其中所述至少一种表面活性剂具有至少 8.0 的亲水-亲油平衡值。

57. 如权利要求 49 所述的方法，其中所述至少一种表面活性剂选自下组，该组的组成为：至少一种阴离子表面活性剂、至少一种非离子型表面活性剂、至少一种两性离子表面活性剂、至少一种阳离子表面活性剂，或它们的组合。

58. 如权利要求 49 所述的方法，其中所述至少一种表面活性剂包括选自下组的至少一种非离子型表面活性剂，该组的组成为：至少一种聚山梨酯、至少一种泊洛沙姆，或它们的组合。

59. 如权利要求 49 所述的方法，其中所述至少一种表面活性剂包括所述组合物的从大约 15% wt/wt 到大约 31% wt/wt 的至少一种聚山梨酯。

60. 如权利要求 49 所述的方法，其中所述至少一种表面活性剂是聚山梨酯 80。

61. 如权利要求 49 所述的方法，其中所述至少一种表面活性剂包括所述组合物的从大约 0.5% wt/wt 到大约 5% wt/wt 的至少一种泊洛沙姆。

62. 如权利要求 49 所述的方法，进一步包含至少一种抗氧化剂。

63. 如权利要求 49 所述的方法，进一步包含选自下组的至少一种抗氧化剂，该组的组成为：至少一种生育酚、至少一种生育三烯酚，以及它们的组合。

64. 如权利要求 49 所述的方法，进一步包含至少一种生育酚。

65. 如权利要求 49 所述的方法，进一步包含所述组合物的从大约 0.01% (wt/wt) 到大约 5% (wt/wt) 的至少一种生育酚。

66. 如权利要求 49 所述的方法，进一步包含至少一种萜。

67. 如权利要求 49 所述的方法，进一步包含基本上纯的 d- 柠檬烯。

68. 如权利要求 49 所述的方法，进一步包含所述组合物的从大约 0.1% (wt/wt) 到大约 5% (wt/wt) 的基本上纯的 d- 柠檬烯。

69. 如权利要求 49 所述的方法，进一步包含所述组合物的从大约 0.1% (wt/wt) 到大约 5% (wt/wt) 的天然橙油。

70. 如权利要求 49 所述的方法，其中所述组合物在一种水性介质中形成胶束。

71. 如权利要求 49 所述的方法，其中所述组合物在一种具有酸性 pH 的水性介质中形成胶束。

72. 如权利要求 49 所述的方法，其中所述组合物在 0.1N HCl 中形成胶束。

73. 如权利要求 70 所述的方法，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

74. 如权利要求 71 所述的方法，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

75. 如权利要求 72 所述的方法，其中所述胶束具有从大约 1μm 到大约 10μm 的直径。

76. 如权利要求 47 所述的方法，其中所述组合物与食物一起或不与食物一起给予至人类受试者。

77. 如权利要求 49 所述的方法，其中所述至少一种 ω-3 脂肪酸酯主要由至少一种乙酯组成。

78. 如权利要求 49 所述的方法，其中所述心血管病症或失调选自下组，该组的组成为心脏和血管的失调，包括例如高血压、高脂血症、高甘油三酯血症、动脉粥样硬化、短暂性脑缺血发作、收缩功能障碍、舒张功能障碍、动脉瘤、主动脉夹层、心肌缺血、急性心肌梗死 (AMI)、急性 ST 段抬高型心肌梗死 (STEMI)、急性非 ST 段抬高型心肌梗死 (NSTEMI)、心绞痛、不稳定型心绞痛 (UA)、稳定型心绞痛 (SA)、心肌梗死、充血性心力衰竭、扩张性充血性心肌病、肥厚型心肌病、限制型心肌病、肺原性心脏病、心律失常、瓣膜性心脏病、心内膜炎、肺栓塞、静脉血栓形成、周围血管疾病、和外周动脉疾病。

79. 如权利要求 49 所述的组合物，其中所述心血管病症或失调选自下组，该组的组成为：高血压、高脂血症、和它们的组合。

80. 如权利要求 49 所述的组合物，其中所述心血管病症或失调选自下组，该组的组成为：高血压、高脂血症、和它们的组合。

81. 如权利要求 49 所述的组合物，其中所述心血管病症或失调是高甘油三酯血症。

82. 如权利要求 81 所述的方法，其中在向人类受试者给予所述组合物大约 30 天之内降低血清甘油三酯总量的至少 20％。

83. 如权利要求 82 所述的方法，其中在给予所述组合物的三十天之内，在所述人类受试者的血液中的血清低密度脂蛋白 (LDL) 的总浓度基本上没有增加。

84. 如权利要求 54 所述的方法，其中该组合物的所述治疗有效量包括至少 0.5g/ 天。

85. 如权利要求 54 所述的方法，其中在给予之后大约四小时之内，所述受试者的血清具有浓度为至少大约 20nmol/mL 的 ω-3 脂肪酸酯。

86. 如权利要求 49 所述的方法，其中所述组合物是以口服方式给予受试者的。

87. 如权利要求 49 所述的方法，其中所述组合物是作为一种凝胶或液体胶囊给予受试者的。

88. 如权利要求 49 所述的方法，其中所述组合物是作为肠胃外组合物给予受试者的。

89. 如权利要求 49 所述的方法，其中所述组合物与非 -ω-3 脂肪酸酯降脂剂组合给予人类受试者。

90. 如权利要求 89 所述的方法，其中所述非 -ω-3 脂肪酸酯降脂剂选自下组，该组的组成为 :胆固醇吸收抑制剂、胆汁酸螯合剂 / 树脂、他汀类药物、烟酸和衍生物、MTP 抑制剂、贝特类和 CETP 抑制剂。

91. 如权利要求 49 所述的方法，其中所述组合物在给予至具有≥ 155mg TG/dL 血清的血清 TG 水平的人类受试者时降低了所述受试者的 TG 水平的至少大约 20％。

92. 一种包含如权利要求 1 所述的组合物的药盒，该组合物与关于使用所述组合物治疗心血管病症或失调的说明书一起包装。

93. 如权利要求 92 所述的药盒，其中所述组合物呈包装在泡罩包装中或瓶子中的凝胶或液体胶囊的剂型。

94. 如权利要求 92 所述的药盒，其中所述说明书包括与食物一起或不与食物一起给予所述组合物。

95. 如权利要求 92 所述的药盒，其中所述说明书包括向具有≥ 150mg TG/dL 的血清 TG 水平的人类受试者与食物一起给予或不与食物一起给予所述组合物。

96. 一种包含如权利要求 32 所述的组合物的药盒，该组合物与关于使用该组合物治疗心血管病症或失调的说明书一起包装。

97. 如权利要求 96 所述的药盒，其中所述组合物呈包装在泡罩包装中或瓶子中的凝胶或液体胶囊的剂型。

98. 如权利要求 96 所述的药盒，其中所述说明书包括与食物一起或不与食物一起给予所述组合物。

99. 如权利要求 96 所述的药盒，其中所述说明书包括向具有≥ 150mg TG/dL 的血清 TG 水平的人类受试者与食物一起给予或不与食物一起给予所述组合物。

100. 一种功能食品，该功能食品包含一种可食用固体和一种药用组合物，该药用组合物包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂 ;其中所述至少一种 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物，并且其中所述组合物基本上不含 ω-3 游离脂肪酸。

101. 一种功能食品，该功能食品包含一种可食用液体和一种药用组合物，该药用组合物包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂；其中所述至少一种 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物，并且其中所述组合物基本上不含 ω-3 游离脂肪酸。

102. 一种功能食品，该功能食品包含一种可食用固体和一种药用组合物，该药用组合物包含处于大于 2:1 到不大于 3.4:1 比率的 EPA 乙酯和 DHA 乙酯、从大约 15％ (wt/wt) 到大约 31％ (wt/wt) 的聚山梨酯 80、以及从大约 0.5％ (wt/wt) 到大约 5％ (wt/wt) 的普朗尼克 F87；其中所述 EPA 乙酯和 DHA 乙酯构成至少大约 40％ (wt/wt) 的该组合物，并且所述组合物基本上不含 ω-3 游离脂肪酸。

103. 一种功能食品，该功能食品包含一种可食用液体和一种药用组合物，该药用组合物包含处于大于 2:1 到不大于 3.4:1 比率的 EPA 乙酯和 DHA 乙酯、从大约 15％ (wt/wt) 到大约 31％ (wt/wt) 的聚山梨酯 80、以及从大约 0.5％ (wt/wt) 到大约 5％ (wt/wt) 的普朗尼克 F87；其中所述 EPA 乙酯和 DHA 乙酯构成至少大约 40％ (wt/wt) 的该组合物，并且其中所述组合物不含 ω-3 游离脂肪酸。

104. 一种治疗处于心血管疾病风险或患有心血管疾病的人类受试者的方法，该方法包括给予有效量的根据权利要求 100 所述的功能食品。

105. 一种治疗处于心血管疾病风险或患有心血管疾病的人类受试者的方法，该方法包括给予有效量的根据权利要求 101 所述的功能食品。

106. 一种治疗处于心血管疾病风险或患有心血管疾病的人类受试者的方法，该方法包括给予有效量的根据权利要求 102 所述的功能食品。

107. 一种治疗处于心血管疾病风险或患有心血管疾病的人类受试者的方法，该方法包括给予有效量的根据权利要求 103 所述的功能食品。

108. 一种药用组合物，该药用组合物包含处于大于 2:1 到不大于 3.4:1 重量与重量比率 (EPA:DHA) 的至少一种 EPA 酯和至少一种 DHA 酯，其中所述组合的至少一种 EPA 酯和所述至少一种 DHA 酯构成按重量计从大约 40％到大约 95％的所述组合物，并且其中所述组合物不含除了 ω-3 脂肪酸酯以外的活性成分。

109. 如权利要求 108 所述的方法，其中该组合物进一步包含至少一种萜。

110. 如权利要求 108 所述的组合物，其中该组合物进一步包含所述组合物的从大约 0.1％ (wt/wt) 到大约 5％ (wt/wt) 的基本上纯的 d- 柠檬烯。

111. 一种治疗需要这样的治疗的受试者中的心血管病症或失调的方法，所述方法包括向所述受试者给予治疗有效量的一种组合物，该组合物包含处于大于 2:1 到不大于 3.4:1 重量与重量比率 (EPA:DHA) 的至少一种 EPA 酯和至少一种 DHA 酯，其中所述组合的至少一种 EPA 酯和所述至少一种 DHA 酯构成按重量计从大约 40％到大约 95％的该组合物，并且其中所述组合物基本上不含除了 ω-3 脂肪酸酯以外的活性成分。

112. 如权利要求 111 所述的方法，其中所述组合物进一步包含至少一种萜。

113. 如权利要求 111 所述的方法，其中所述组合物进一步包含所述组合物的从大约 0.1％ (wt/wt) 到大约 5％ (wt/wt) 的基本上纯的 d- 柠檬烯。

114. 一种包含至少一种 ω-3 脂肪酸酯和至少一种萜的药用组合物；其中所述至少一种 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物并且基本上不含除了所述至少一

种 ω-3 脂肪酸酯以外的活性成分。

115. 如权利要求 114 所述的组合物，其中该至少一种萜是 d- 柠檬烯。

116. 如权利要求 114 所述的组合物，其中该至少一种萜是基本上纯的 d- 柠檬烯。

117. 如权利要求 114 所述的组合物，其中该至少一种萜是至少 95％纯的 d- 柠檬烯。

118. 一种包含 EPA 乙酯和 DHA 乙酯的混合物和至少一种萜的组合物，其中 EPA:DHA 的比率是大约 2.4:1，并且其中所述组合的 EPA 乙酯和 DHA 乙酯构成从大约 40％ (wt/wt) 到大约 95％ (wt/wt) 的所述组合物，并且不含除了所述 EPA 酯和 DHA 酯以及至少一种萜以外的活性成分。

119. 如权利要求 118 所述的组合物，其中该至少一种萜是 d- 柠檬烯。

120. 如权利要求 118 所述的组合物，其中该至少一种萜是基本上纯的 d- 柠檬烯。

121. 如权利要求 118 所述的药用组合物，其中该至少一种萜是至少 95％纯的 d- 柠檬烯。

ω-3 脂肪酸酯组合物

[0001] 相关申请的交叉引用

[0002] 本申请要求于 2012 年 3 月 30 日提交的美国临时专利申请号 61/618,161 的优先权益。

背景技术

[0003] 根据世界卫生组织 (WHO) 关于心血管疾病 (CVD) 的简报所知，CVD 是全球的头号死因。(简报号 317,2012 年 9 月访问 (http://www.who.int/mediacentre/factsheets/fs317/en/index.html,2013 年 1 月 31 日)。据 WHO 估计，在 2008 年估计有 1730 万人死于 CVD，占全球所有死亡的 30％。在这些死亡中，估计有 730 万是由于冠心病 (CHD) 所致，并且 620 万是由于中风所致。WHO 还估计，到 2030 年，几乎 2500 万人将死于 CVD，主要死于心脏病和中风。据全球疾病负担研究 (The Global Burden of Disease Study) 估计，在 1990 年，在 620 万 CHD 全球死亡人数中，发展中国家占 350 万。(穆雷 (Murray)CJL 和洛佩斯 (Lopez)AD. “全球疾病负担，在 1990 年并预计到 2020 年，源于疾病、损伤和风险因子的死亡率和残疾的综合评估”(The Global Burden of Disease A Comprehensive Assessment of Mortality and Disability from Disease, Injuries and Risk Factors in 1990and Projected to 2020)，波士顿 (Boston)，麻省剑桥：哈佛大学出版社 (Ma Harvard University Press) ;1996)。这些预测估计，在 2020 年由于 CHD 所致的 1110 万死亡人数中，这些国家将占据 780 万。发达国家也并非可免于 CHD。例如，在美国和欧洲，CHD 仍然是首要的死亡与残疾的单原因。2005 年，在美国大约每 5 人中就有 1 人的死亡由 CHD 引起。(赫伦 (Heron)MP 等人，“死亡 :2006 年的初步数据”(Deaths preliminary data for 2006)，美国国家统计报告 (Natl.Vital.Stat.Rep.)2008 ;56:1-52)。根据美国疾病控制与预防中心的报告，它是美国的首要死亡原因。在特定的一年中发生冠心病事件的人大约 37％将死于该事件。虽然在欧洲已经实现 CVD 有关死亡率的大幅下降，CVD 仍然占了所有女性死亡人数的 54％，以及所有男性死亡人数的 43％。

[0004] CVD 与许多风险因子有关。在这些风险因子中，高脂血症 (例如，高甘油三酯血症) 和高胆固醇血症是 CVD 的重要指标。正因为这样，当前使用含有 ω-3 脂肪酸酯例如 EPA 和 DHA 的乙酯的膳食补充剂、营养保健品、和处方药来治疗 CVD，并且尤其是用于降低已升高的甘油三酯。

[0005] 然而，含有 ω-3 脂肪酸酯的膳食补充剂、营养保健品、和处方药的给予存在重大挑战。例如，当口服给予时，当前的含有 ω-3 脂肪酸酯的膳食补充剂、营养保健品、和处方药具有可变的吸收和效力。具体而言，当前的组合物具有显著的“食物效应”，当在禁食的时候或者与低脂肪餐一起服用时，具有不良的吸收。当与油脂食物一起服用时，ω-3 脂肪酸酯的吸收部分地由于释放在胃中的胆盐的存在而得以改进，这些胆盐有助于 ω-3 脂肪酸酯的吸收。

[0006] 为了克服低吸收，可以用具有较大量 ω-3 脂肪酸酯的组合物给予患者，但是，由于与这样的组合物普遍相关的副作用，对于这种方法存在着实际限制。随着时间过去发生

的 ω-3 脂肪酸酯的氧化降解可以导致在给药之后的令人不愉快的余味，尤其是在大量消费时。嗳气和胃不适是另外的令人不愉快的副作用，这些副作用与 ω-3 脂肪酸酯的消费相关。在消费之后，ω-3 脂肪酸酯倾向于漂浮在胃中的液体内容物上，形成一个阻止小气泡通过的层。当足够的气体以已经积累到克服该油层的表面张力时，人就会打嗝。打出的嗝常常含有鱼腥味和臭味。

[0007] 相应地已知的是，与给予当前的包含 ω-3 脂肪酸酯的组合物相关联的副作用（例如，易受到食物效应的影响、达到效果需要大剂量、以及因而发生的余味、令人不愉快的气味、和嗳气）显著降低了患者的依从性。

[0008] 虽然实行健康的生活方式可以降低 CVD 的发病率，控制 CVD 的新治疗途径是正当的。这些新的途径可包括新药的发现或改进用于治疗 CVD 的当前药物。然而，发现新药的成本高，并且最终成功是不确定的。相应地，应当开发以证实的安全与有效状况递送当前药物的新的或更有效的方式。因而，对于改进的包含 ω-3 脂肪酸酯例如 EPA 和 DHA 的乙酯的组合物存在着需要，这些组合物较少受到食物效应影响并且以更低的剂量达到高效力。在理想的情况下，这种改进的组合物在患者中将令人不愉快的气味和 / 或令人不愉快的余味、和 / 或嗳气降低到最低限度或将其消除。具有副作用减少的这种改进的组合物将提高患者的依从性并且更有效地对付与心血管疾病有关的风险因子。

发明内容

[0009] 在此处提供的所有实施例中，所有组合物均不含 ω-3 游离脂肪酸。在某些实施例中，在此提供的是包含与至少一种表面活性剂组合的 EPA 酯和 DHA 酯的组合物。在某些实施例中，EPA 酯与 DHA 酯的比率是从大于 2:1 到不大于 3.4:1。某些实施例提供从大约 2:1 到大约 3.4:1 的 EPA 酯与 DHA 酯的比率。在某些实施例中，在此提供的是包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂的组合物。在某些实施例中，该 ω-3 脂肪酸酯选自下组，该组的组成为：十六碳三烯酸、α - 亚麻酸、十八碳四烯酸、二十碳三烯酸、二十碳五烯酸、二十一碳五烯酸、二十二碳五烯酸、二十二碳六烯酸、二十四碳五烯酸、二十四碳六烯酸、或它们的组合。某些实施例提供包含所述 ω-3 脂肪酸酯的乙酯衍生物的组合物，任选地与至少一种表面活性剂、至少一种萜、至少一种抗氧化剂、或它们的组合相组合。某些实施例还提供具有从大约 2:1 到大约 3.4:1 比率的不同 ω-3 脂肪酸酯的组合。其他实施例要求大于 2:1 但不大于 3.4:1 的比率。典型地，该比率是大约 2.4:1。某些实施例提供用于治疗可以通过给予所述 ω-3 脂肪酸酯治疗的多种病症或失调的方法，这些 ω-3 脂肪酸酯具有在此描述的组成，包含所描述的比率，任选地具有至少一种表面活性剂、至少一种萜、至少一种抗氧化剂、或它们的组合。在此描述的这些组合物将发现于目前市场上的含有 ω-3 脂肪酸酯的组合物的若干副作用降低到最低限度，这些 ω-3 脂肪酸酯可阻止人类受试者依从于给药方案，该给药方案是用于治疗通过给予 ω-3 脂肪酸酯可治疗的病症或失调必需的。在某些实施例中，在与或不与食物一起给予的情况下，当向需要这种给予的人类受试者给予作为在此描述的某些组合物时，所述 ω-3 脂肪酸酯的生物利用度是基本上相同的，即，基本上不依赖于食物效应。

[0010] 因而，某些实施例要求包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂的药用组合物，其中所述至少一种 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物。

[0011] 某些实施例要求包含第一 ω-3 脂肪酸酯和第二 ω-3 脂肪酸酯的药用组合物，该第一 ω-3 脂肪酸酯选自下组，该组的组成为：十六碳三烯酸、α-亚麻酸、十八碳四烯酸、二十碳三烯酸、二十碳五烯酸、二十一碳五烯酸、二十二碳五烯酸、二十二碳六烯酸、二十四碳五烯酸、二十四碳六烯酸，该第二 ω-3 脂肪酸酯选自下组，该组的组成为：十六碳三烯酸、α-亚麻酸、十八碳四烯酸、二十碳三烯酸、二十碳五烯酸、二十一碳五烯酸、二十二碳五烯酸、二十二碳六烯酸、二十四碳五烯酸、二十四碳六烯酸，使得选定的第一和第二 ω-3 脂肪酸酯彼此不相同，并且第一和第二 ω-3 脂肪酸酯的比率为大于 2:1 到不大于 3.4:1 的比率（第一 ω-3 脂肪酸酯：第二 ω-3 脂肪酸酯）；其中组合的第一和第二 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物，并且其中所述组合物基本上不含除了所述 ω-3 脂肪酸酯以外的活性成分。

[0012] 某些实施例要求使用至少一种 ω-3 脂肪酸酯。典型地，该 ω-3 脂肪酸酯是一种乙酯。

[0013] 某些实施例要求包含至少一种 ω-3 脂肪酸酯和至少一种萜的药用组合物；其中所述至少一种 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物并且基本上不含除了 ω-3 脂肪酸酯以外的活性成分。在某些实施例中，该至少一种 ω-3 脂肪酸酯构成大约 40％、45％、50％、55％、60％、65％、70％、75％。该萜典型地但不必需地是 d- 柠檬烯。在某些其他实施例中，这样的组合物包含天然橙油。

[0014] 某些实施例提供包含 EPA 乙酯和 DHA 乙酯以及至少一种萜的组合物，其中 EPA:DHA 的比率是大约 2.4:1，并且其中所述组合的 EPA 乙酯和 DHA 乙酯构成从大约 40％ (wt/wt) 到大约 95％ (wt/wt) 的所述组合物。在某些实施例中，组合的 EPA 乙酯和 DHA 乙酯构成大约 40％ (wt/wt) 的所述组合物。该萜典型地但不必需地是 d- 柠檬烯。在某些其他实施例中，这样的组合物包含天然橙油。

[0015] 在包含基本上纯的 d- 柠檬烯的实施例中，该 d- 柠檬烯是从大约 95％到大约 98％纯的。在某些实施例中，该基本上纯的 d- 柠檬烯是至少 95％、96％、97％或 98％纯的。

[0016] 在某些实施例中，该 ω-3 脂肪酸酯选自下组，该组的组成为：至少一种 EPA 酯、至少一种 DHA 酯或它们的组合，并且包含至少一种表面活性剂。在某些实施例中，该至少一种 EPA 酯和至少一种 DHA 酯是基本上纯的。某些实施例还提供包含处于从大约 2:1 到大约 3.4:1 的比率的至少一种 EPA 酯和至少一种 DHA 酯的组合物，其基本上不含除了 ω-3 脂肪酸酯以外的活性成分。还描述了包含其他比率的组合物。某些组合物也可以不含天然橙油或 d- 柠檬烯。在某些实施例中，这些 ω-3 脂肪酸酯构成至少 40％的该组合物。典型地，这些 ω-3EPA 酯和 DHA 酯是乙酯。在此描述的某些组合物在一种水性介质中形成胶束并且没有食物效应。当某些组合物与食物一起给予或不与食物一起给予时，都基本上没有食物效应。在此还提供了使用描述的这些组合物治疗心血管病症或失调的方法。当与给予现有技术的组合物比较时，在此描述的这些组合物将副作用降低到最低限度或将其消除。还提供了包装的 ω-3 脂肪酸酯的组合物或药盒，其包含一种或多种单位剂型连同有关使用这些组合物的说明书。

[0017] 相应地，在至少一个实施例中提供了包含处于大于约 2:1 到不大于约 3.4:1(EPA:DHA) 的重量与重量比率的至少一种 EPA 酯和至少一种 DHA 酯以及至少一种表面活性剂的药用组合物，其中所述组合的 EPA 酯和 DHA 酯构成按重量计从大约 40％到大约

85％的该组合物。在某些这样的实施例中，组合的 EPA 乙酯和 DHA 乙酯构成大约 50％ (wt/wt) 的所述组合物。

[0018] 在至少一个其他实施例中提供了包含处于从大于约 2:1 到大约 3.4:1(EPA:DHA) 的重量与重量比率的至少一种 EPA 酯和至少一种 DHA 酯以及至少一种表面活性剂的药用组合物，其中所述组合的 EPA 酯和 DHA 酯构成按重量计从大约 40％到大约 85％的该组合物。在某些这样的实施例中，组合的 EPA 乙酯和 DHA 乙酯构成大约 50％ (wt/wt) 的所述组合物。

[0019] 在至少一个其他实施例中提供了包含处于大于 2:1 到不大于 3.4:1(EPA:DHA) 的重量与重量比率的至少一种 EPA 酯和至少一种 DHA 酯以及至少一种表面活性剂的药用组合物，其中所述组合的 EPA 酯和 DHA 酯构成按重量计从大约 40％到大约 85％的该组合物。在某些这样的实施例中，组合的 EPA 乙酯和 DHA 乙酯构成大约 50％ (wt/wt) 的所述组合物。

[0020] 在至少一个其他实施例中提供了包含处于大于 2:1 到不大于 3.4:1(EPA:DHA) 的重量与重量比率的至少一种 EPA 酯和至少一种 DHA 酯以及至少一种表面活性剂的药用组合物，其中所述组合的 EPA 酯和 DHA 酯构成按重量计从大约 40％到大约 85％的该组合物，并且其中当该组合物与食物一起给予或不与食物一起给予至需要这种给予的人类受试者时，都基本上没有食物效应。在某些这样的实施例中，组合的 EPA 乙酯和 DHA 乙酯构成大约 50％ (wt/wt) 的所述组合物。

[0021] 在至少一个实施例中，在此描述的这些组合物包含基本上纯的至少一种 EPA 酯和 / 或至少一种 DHA 酯。

[0022] 在至少一个实施例中，在此描述的这些组合物主要由至少一种 EPA 酯和 / 或至少一种 DHA 酯组成。

[0023] 在某些实施例中，构成该组合物的该 EPA 酯和 DHA 酯的任一者或每一者是乙酯。

[0024] 在某些实施例中，在此描述的这些组合物包含基本上纯的 EPA 乙酯和 / 或基本上纯的 DHA 乙酯。

[0025] 在某些实施例中，在此描述的这些组合物主要由基本上纯的 EPA 乙酯和 / 或基本上纯的 DHA 乙酯组成。

[0026] 在某些实施例中，构成该组合物的该 EPA 酯和该 DHA 酯的比率是大约 2.4:1(EPA 酯 :DHA 酯)。

[0027] 某些实施例要求也包含天然橙油的组合物，该天然橙油占所述组合物的从大约 0.1％到大约 5％ (wt/wt)。在包含天然橙油的实施例中，该天然橙油以该组合物的大约 1.6％ (wt/wt) 存在。某些其他实施例包含从大约 0.1％到大约 5％的基本上纯的 d- 柠檬烯。在包含基本上纯的 d- 柠檬烯的实施例中，该 d- 柠檬烯以该组合物的大约 1.5％ (wt/wt) 存在。

[0028] 在某些实施例中，在给予至受试者之时，在此描述的这些组合物的药理效应基本上不受食物效应的影响。

[0029] 在至少一个实施例中，提供了一种药用混合脂肪酸组合物，其中，a) 按重量计至少 80％的该组合物是由处于从 1:2 到 2:1 的 EPA:DHA 重量比的 (全顺式 ω-3)-5,8,11,14,17- 二十碳五烯酸 (EPA) 和 (全顺式 ω-3)-4,7,10,13,16,19- 二十二碳六烯酸 (DHA) 的组合组成的 ;b)(全顺式 ω-3)-6,9,12,15,18- 二十一碳五烯酸是以按重量计至少百分之一的量存在 ;并且 c) 提供了至少一种表面活性剂。这些组合物可任选地进

一步包含所述组合物的从大约0.1%到大约5%(wt/wt)的天然橙油或从大约0.1%到大约5%(wt/wt)的基本上纯的d-柠檬烯。该天然橙油典型地以所述组合物的大约1.6%(wt/wt)存在并且d-柠檬烯典型地以该组合物的大约1.5%(wt/wt)存在。

[0030] 在至少一个实施例中,提供了一种用于治疗或预防多种CVD风险因子的至少一种的混合脂肪酸组合物,其中a)按重量计至少80%的该组合物是由ω-3脂肪酸组成的;b)按重量计该组合物的至少80%的总脂肪酸含量是由处于从1:2到2:1的EPA:DHA重量比的(全顺式ω-3)-5,8,11,14,17-二十碳五烯酸(EPA)和(全顺式ω-3)-4,7,10,13,16,19-二十二碳六烯酸(DHA)的组合组成的,c)除了EPA和DHA以外的ω-3脂肪酸以总脂肪酸的按重量计1.5%的量存在;并且c)提供了至少一种表面活性剂。这些组合物可任选地进一步包含所述组合物的从大约0.1%到大约5%(wt/wt)的天然橙油或从大约0.1%到大约5%(wt/wt)的基本上纯的d-柠檬烯。该天然橙油典型地以所述组合物的大约1.6%(wt/wt)存在并且d-柠檬烯典型地以该组合物的大约1.5%(wt/wt)存在。

[0031] 在至少一个实施例中,提供了一种药用混合脂肪酸组合物,其中,a)按重量计至少80%的该组合物是由是由处于从1:2到2:1的EPA:DHA重量比的(全顺式ω-3)-5,8,11,14,17-二十碳五烯酸(EPA)和(全顺式ω-3)-4,7,10,13,16,19-二十二碳六烯酸(DHA)的组合组成的,b)按重量计至少3%的该组合物是由除了EPA和DHA以外具有18、20、21、或22个碳原子的ω-3脂肪酸组成的,并且c)提供了至少一种表面活性剂。这些组合物可任选地进一步包含所述组合物的从大约0.1%到大约5%(wt/wt)的天然橙油或从大约0.1%到大约5%(wt/wt)的基本上纯的d-柠檬烯。该天然橙油典型地以所述组合物的大约1.6%(wt/wt)存在并且d-柠檬烯典型地以该组合物的大约1.5%(wt/wt)存在。

[0032] 在至少一个实施例中,提供了一种药用混合脂肪酸组合物,其中,a)按重量计至少90%的该组合物是由长链多不饱和ω-3脂肪酸组成的;b)按重量计至少80%的该组合物是由是由处于从1:1到2:1的EPA:DHA重量比的(全顺式ω-3)-5,8,11,14,17-二十碳五烯酸(EPA)和(全顺式ω-3)-4,7,10,13,16,19-二十二碳六烯酸(DHA)的组合组成的,其中EPA构成按重量计40%到60%的该组合物,并且DHA构成按重量计25%到45%的该组合物;c)按重量计至少4.5%的该组合物是由除了EPA和DHA以外具有18、20、21、或22个碳原子的ω-3脂肪酸组成的;d)按重量计从1%到4%的该组合物是由(全顺式ω-3)-6,9,12,15,18-二十一碳五烯酸组成的;e)至少一种表面活性剂;和f)该组合物呈口服剂型形式并且包括包括有效量的药学上可接受的抗氧化剂。这些组合物可任选地进一步包含所述组合物的从大约0.1%到大约5%(wt/wt)的天然橙油或从大约0.1%到大约5%(wt/wt)的基本上纯的d-柠檬烯。该天然橙油典型地以所述组合物的大约1.6%(wt/wt)存在并且d-柠檬烯典型地以该组合物的大约1.5%(wt/wt)存在。

[0033] 应当注意的是,在所有包含在此描述的组合物的这些实施例中,构成该组合物的所有成分的总和不超过100%。

[0034] 在某些实施例中提供了一种包含处于大约3.5:1到大约5:1的重量与重量比率的EPA和DHA和至少一种表面活性剂的药用或药物组合物,并且其中该组合物含有按重量计大于84%的组合的EPA和DHA。这些组合物可任选地进一步包含所述组合物的从大约0.1%

到大约 5％ (wt/wt) 的天然橙油或从大约 0.1％到大约 5％ (wt/wt) 的基本上纯的 d- 柠檬烯。该天然橙油典型地以所述组合物的大约 1.6％ (wt/wt) 存在并且 d- 柠檬烯典型地以该组合物的大约 1.5％ (wt/wt) 存在。

[0035] 某些实施例提供包含按重量计至少大约 96％的二十碳五烯酸乙酯 (乙基 -EPA)、至少一种表面活性剂、基本上没有二十二碳六烯酸 (DHA) 或其酯的某些组合物。这些组合物可任选地进一步包含所述组合物的从大约 0.1％到大约 5％ (wt/wt) 的天然橙油或从大约 0.1％到大约 5％ (wt/wt) 的基本上纯的 d- 柠檬烯。该天然橙油典型地以所述组合物的大约 1.6％ (wt/wt) 存在并且 d- 柠檬烯典型地以该组合物的大约 1.5％ (wt/wt) 存在。

[0036] 在至少一个实施例中，提供了用于治疗以下失调的方法 ：代谢综合征、黄斑变性、ω-3 缺乏、认知损害，包括作为结果的手术或外伤性脑损伤 (例如像，由于脑震荡)、重性抑郁、自杀、产后抑郁、炎症、原发性硬化性胆管炎、女性边缘型人格障碍、乳腺癌、非酒精性脂肪酸肝病，以及用于改善儿童的认知和行为。可以通过向需要这种给药的受试者 (典型地，人类) 给予在此描述的这些组合物治疗来这些病症或失调。

[0037] 在至少一个实施例中，提供了用于治疗在需要这样的治疗的受试者中的至少一种心血管病症或失调的方法，所述方法包括向受试者给予在此描述的包含治疗有效量的 ω-3 脂肪酸酯和至少一种表面活性剂的至少一种组合物。

[0038] 在至少一个实施例中提供了用于治疗至少一种心血管病症或失调的方法，例如但不限于心脏和血管的失调，包括例如高血压、高脂血症、高甘油三酯血症、动脉粥样硬化、短暂性脑缺血发作、收缩功能障碍、舒张功能障碍、动脉瘤、主动脉夹层、心肌缺血、急性心肌梗死 (AMI)、急性 ST 段抬高型心肌梗死 (STEMI)、急性非 ST 段抬高型心肌梗死 (NSTEMI)、心绞痛、不稳定型心绞痛 (UA)、稳定型心绞痛 (SA)、心肌梗死、充血性心力衰竭、扩张性充血性心肌病、肥厚型心肌病、限制型心肌病、肺原性心脏病、心律失常、瓣膜性心脏病、心内膜炎、肺栓塞、静脉血栓形成、周围血管疾病、和外周动脉疾病。该方法包括向需要治疗的受试者给予治疗有效量的在此描述的组合物。

[0039] 在至少一个实施例中，提供了用于治疗高血压和 / 或高脂血症的方法。

[0040] 在至少一个其他实施例中，提供了用于治疗高甘油三酯血症的方法。

[0041] 在某些实施例中，在给予在此描述的这些组合物的某些实施例之后大约 30 天之内，在给药方案的开始时具有≥ 150mg TG/dL 的血清的人类受试者的血液中的甘油三酯类 (TG) 的总量被降低至少 20％。

[0042] 在至少一个其他的实施例中，提供了一种用于治疗具有≥ 150mg TG/dL 的血清的人类受试者的方法，所述方法包括向该人类受试者给予至少一个实施例的包含治疗有效量的 ω-3 脂肪酸酯的在此描述的组合物。

[0043] 还提供了其中在此描述的这些组合物被包装在一起作为一个药盒的实施例，该药盒带有关于怎样使用这些组合物治疗心血管病症或失调的说明书。

[0044] 在某些实施例中，该表面活性剂选自下组，该组的组成为 ：至少一种非离子型表面活性剂、阳离子表面活性剂、阴离子表面活性剂、两性离子表面活性剂、或它们的组合。

[0045] 在某些实施例中，该表面活性剂选自下组，该组的组成为 ：至少一种阴离子表面活性剂、至少一种非离子型表面活性剂，和它们的组合。

[0046] 在包含至少一种表面活性剂的某些实施例中，该至少一种表面活性剂具有大约

8.0 的亲水 - 亲油平衡值 (HLB)。

[0047] 在包含至少一种表面活性剂的某些实施例中，该表面活性剂可以是选自下组的非离子型表面活性剂，该组的组成为：至少一种聚山梨酯、至少一种泊洛沙姆、和它们的组合。

[0048] 在某些实施例中，该至少一种表面活性剂包括以该组合物的从大约 15% wt/wt 到大约 31% wt/wt 存在的聚山梨酯。在某些实施例中，该聚山梨酯是聚山梨酯 80。

[0049] 在某些其他实施例中，该至少一种表面活性剂包括以该组合物的从大约 0.1% wt/wt 到大约 5% wt/wt 存在的泊洛沙姆。

[0050] 在某些实施例中，在此描述的这些组合物包含聚山梨酯 80 和泊洛沙姆普朗尼克 F 87[$(HO(C_2H_4O)_{64}(C_3H_6O)_{37}(C_2H_4O)_{64}H$] 的组合。

[0051] 在某些实施例中，该组合物进一步包括至少一种抗氧化剂。在这样的实施例中，该至少一种抗氧化剂选自下组，该组的组成为：一种生育酚、一种生育三烯酚、或它们的组合。在这样的实施例中，该生育酚、生育三烯酚或它们的组合以这些组合物的按重量计从大约 0.01%到大约 5%存在。在某些这样的实施例中，这些生育酚、生育三烯酚或它们的组合可以大约按重量计这些组合物的 0.01%、0.05%、0.1%、0.2%、0.3%、0.4%、0.5%、0.6%、0.7%、0.8%、0.9%、1%、1.5%、2%、2.5%、3%、3.5%、4%、4.5%或 5%存在。在某些这样的实施例中，这些生育酚、生育三烯酚或它们的组合可以这些组合物的按重量计大约 0.4%存在。在某些实施例中，该生育酚、生育三烯酚或它们的组合以该组合物的按重量计大约 0.4%存在。在进一步包括至少一种抗氧化剂的某些实施例中，该抗氧化剂是该组合物的按重量计大约 0.4%的生育酚。

[0052] 在某些实施例中，该组合物在一种水性介质中自胶束化 (self-micellize)。在某些其他实施例中，该水性介质是水。在某些其他实施例中，该水性介质具有酸性 pH。在某些其他实施例中，该水性介质是 0.1N HCl。

[0053] 在某些实施例中，在此描述的这些组合物在一种水性介质中自胶束化，其中这些胶束具有从大约 1μm 到大约 10μm 的直径。在某些实施例中，在此描述的这些组合物在一种具有酸性 pH 的水性介质中自胶束化，其中这些胶束具有从大约 1μm 到大约 10μm 的直径。在某些其他实施例中，在此描述的这些组合物在 0.1N HCL 中自胶束化，其中这些胶束具有从大约 1μm 到大约 10μm 的直径。在某些实施例中，这些胶束具有大约 1、2、3、4、5、6、7、8、9、或 10μm 的平均直径。

[0054] 在某些实施例中，在此描述的这些组合物可以与食物一起或不与食物一起给予至需要这样的给予的人类受试者，其中构成这些组合物的这些 ω-3 脂肪酸酯的生物利用度基本上不受食物效应的影响。

[0055] 当与给予基本上不含表面活性剂的包含 ω-3 脂肪酸酯的组合物相比较时，某些实施例提供将由于给予本披露的组合物所致的至少一种副作用降低至最低限度或将其消除的组合物。在其他实施例中，这些副作用的非限制性实例包括反流、频繁嗳气、胃食管反流病 (GERD)、胃气胀、肠积气增加、鱼腥味道 (fish taste)、鱼腥呼吸 (fishy breath)、鱼腥气味 (fish smell)、恶心、腹泻，或它们的组合。

[0056] 在某些实施例中，在此描述的这些组合物包含 d- 柠檬烯或天然橙油。当与给予基本上不含 d- 柠檬烯或天然橙油的包含 ω-3 脂肪酸酯的组合物相比较时，这样的组合物可以将由于给予本披露的组合物所致的至少一种副作用降低至最低限度或将其消除。在其他

实施例中，这些副作用的非限制性实例包括反流、频繁嗳气、胃食管反流病 (GERD)、胃气胀、肠积气增加、鱼腥味道 (fish taste)、鱼腥呼吸 (fishy breath)、鱼腥气味 (fish smell)、恶心、腹泻，或它们的组合。

[0057] 在某些实施例中，当与给予至选自具有从大约 155 到大约 199mg TG/dL 的血清、从大约 200 到大约 499mg TG/dL 的血清以及从大约 500mg 或更高的 TG/dL 的血清的个体组成的组的人类受试者时，在此描述的这些组合物将所述受试者的血清 TG 水平降低至少大约 20％。

[0058] 可以向需要这样的给予的人类受试者给予在此描述的这些组合物的某些实施例，其中非 -ω-3 脂肪酸酯降脂剂选自下组，该组的组成为 :胆固醇吸收抑制剂、胆汁酸螯合剂 / 树脂、他汀类药物、烟酸与衍生物、MTP 抑制剂、贝特类 (fibrates) 和 CETP 抑制剂。

[0059] 在某些实施例中，在此描述的这些组合物在给予所述组合物之后大约 30 天之内可以降低在正针对高甘油三酯血症进行治疗的人类受试者的血清中的 TG 的总量的至少大约 20％，其中该人类受试者在给药方案开始时的血液测量值≥ 150mg TG/dL 血清。

[0060] 在至少一个实施例中，在此描述的这些组合物可以按适当的剂型以口服或肠胃外方式给予。当以口服方式给予时，在此描述的这些组合物可以典型地但不必需地呈凝胶或液体胶囊的形式。

[0061] 在某些其他实施例中，提供了用于给予至少大约 0.5g/ 天的某些实施例的在此描述的这些组合物的方法，这些组合物包含所述组合物的按重量计从大约 40％到大约 85％的处于大于 2:1 到不大于 3.4:1 的比率的至少一种 EPA 酯和至少一种 DHA 酯以及至少一种表面活性剂。典型地但不必需地，该酯为一种乙酯，并且该至少一种表面活性剂是聚山梨酯 80、普朗尼克 F87 或它们的组合。在某些这样的实施例中，组合的 EPA 乙酯和 DHA 乙酯构成大约 50％ (wt/wt) 的所述组合物。任选地，该组合物可以进一步包含基本上纯的 d- 柠檬烯或天然橙油。

[0062] 在某些其他实施例中，提供了用于给予至少大约 4g/ 天的某些实施例的在此描述的这些组合物的方法，这些组合物包含二十碳五烯酸乙酯 (乙基 EPA)、至少一种表面活性剂，并且基本上没有二十二碳六烯酸 (DHA)，其中乙基 EPA 构成按重量计至少大约 96％的该组合物中的总 ω-3 脂肪酸酯。在某些实施例中，这样的组合物可以进一步包含天然橙油或基本上纯的 d- 柠檬烯。

[0063] 某些实施例提供在此描述的这些组合物在用于治疗心血管疾病或失调的药剂的制造中的用途。在某些实施例中，该心血管疾病或失调是高脂血症。在某些其他实施例中，该心血管疾病或失调是高胆固醇血症。在某些实施例中，该心血管疾病或失调是高甘油三酯血症。

[0064] 某些实施例提供在此描述的这些组合物在用于治疗心血管疾病或失调的药剂的制造中的用途。在某些实施例中，该心血管疾病或失调是高脂血症。在某些其他实施例中，该心血管疾病或失调是高胆固醇血症。在某些实施例中，该心血管疾病或失调是高甘油三酯血症。

[0065] 在某些实施例中，在给予某些实施例之后大约四小时之内，给予在此描述的这些组合物提供在人类受试者中的血清浓度为至少大约 20nmol/mL 的组合的至少一种 EPA 酯和至少一种 DHA 酯。

[0066] 还提供了包含作为一种或多种单位剂型的这些 ω-3 脂肪酸酯的组合物连同有关使用这些剂型的说明书的药盒。在某些实施例中，在此描述的这些剂型可以与关于使用这些剂型的说明书一起包装为泡罩包装或包装在瓶子中。例如，这些说明书可以提供为一种包装说明书或者直接地为附着到该泡罩包装、瓶子或二级包装上的标签，在该二级包装中具有提供给人类受试者的泡罩包装或瓶子。这些说明书可以包括，例如给药频率、剂型与食物一起或不与食物一起给予、构成这些剂型的活性成分、以及将受益于给予这些剂型的心血管病症或失调。

[0067] 在某些实施例中提供了这样的药盒，其中包含在此描述的这些组合物的某些剂型可以与其他非 -ω-3 脂肪酸酯降脂剂一起包装。这种或这些药盒包含某些实施例的在此描述的这些组合物的一种或多种单位剂型，连同包含非 -ω-3 脂肪酸酯降脂剂的一种或多种单位剂型，以及关于使用这些剂型的说明书。

[0068] 某些实施例提供用于治疗和 / 或预防 CVD 的包含在此描述的这些组合物的一种或多种功能食品。

[0069] 某些实施例提供了通过给予包含在此描述的这些组合物的功能食品用于治疗 CVD 的方法。

[0070] 某些实施例提供了包含在此描述的这些组合物的一种或多种功能食品，以及治疗人类受试者中的高甘油三脂血症的方法。

附图说明

[0071] 图 1 描绘了一个实施例的显微照片。制备了如在此所述的包含胶束的组合物，将其加在载玻片和盖玻片之间，用尼康型三目头 Spot RT3 数字相机 (Nikon Model Trinocular Head and a Spot RT3digital camera) 在 40X 放大倍数下观察，并测量若干代表性胶束的直径。

[0072] 图 2 显示了用于制造在此描述的这些组合物的一个实施例的过程的示意流程图。

[0073] 图 3 显示了用于制造凝胶块的过程的示意流程图，该凝胶块用于包封在此描述的这些组合物的一个实施例。

[0074] 图 4 显示了用于制造一种剂型的包封过程的示意流程图，该剂型包含在此描述的这些组合物的一个实施例。

具体实施方式

[0075] 在此以不同水平的详情描述了本发明的某些方面、方式、实施例、变化和特征，以便提供有关包含 ω-3 脂肪酸酯的组合物的实施例、以及有关使用这样的含有高浓度 ω-3 脂肪酸酯的组合物的方法的进一步理解。在某些实施例中，EPA 酯和 DHA 酯是以特定重量比和相对量存在的。如所提及的，这些组合物对 CVD 的某些风险因子具有有益作用，包括血清甘油三酯和血清胆固醇的降低。

[0076] 定义

[0077] 如在此使用的，术语“组合物”或“制剂”包括包括治疗性组合物和膳食组合物，包括但不限于，膳食补充剂、营养保健品制剂、或药物制剂。此外，术语组合物、膳食补充剂、营养保健品制剂、和药物制剂在此可互换地使用。

[0078] 如在此使用的，术语“EPA”在内地是指(5Z,8Z,11Z,14Z,17Z)-二十碳-5,8,11,14,17-戊烯酸或其衍生物，包括烷基酯，例如像乙酯。

[0079] 如在此使用的，术语“DHA”在内地是指(4Z,7Z,10Z,13Z,16Z,19Z)-二十二碳-4,7,10,13,16,19-六烯酸或其衍生物，包括烷基酯，例如像乙酯。

[0080] 如在此使用的，术语“胶束”(多个胶束、胶粒或分子团)是指已经被装配成大致球形的核/壳结构并且悬浮在水相中的分子聚集体。在水溶液中的典型胶束形成具有亲水性“头”区的聚集体，这些亲水性“头”区域与周围的溶剂接触和/或与一种或多种表面活性剂的极性区接触，从而将疏水区隔离在胶束的中心。胶束在形状上大致呈球形。

[0081] 如在此使用的术语“自胶束化”是指其中在水性介质中形成胶束而不需要引入能量(包括搅拌或剪切)的过程。

[0082] 如在此使用的，术语“水性介质”是指包含水的任何溶液或悬浮液，例如包括但不限于，水本身；磷酸盐缓冲盐水(pH7.4)、雪碧(Sprite)、苹果汁、G-2水果混合饮料、和巧克力奶。在某些实施例中，水性介质包括具有酸性pH的至少一种流体。在某些其他实施例中，水性介质包括生物流体，例如像，但不限于胃酸。在其他实施例中，该水性介质包括含有0.1N HCl的模拟胃酸。

[0083] 如在此使用的，术语“游离脂肪酸”是指已经被修饰或没有附接任何其他基团的一种或多种多不饱和脂肪酸。

[0084] 如在此使用的，术语“酯”是指在多不饱和脂肪酸分子的羧酸基团中的氢被另一个取代基置换。典型的酯对于本领域的技术人员是已知的，其论述由希古契(Higuchi)T等人，“作为递送系统的药物前体”(Pro-drugs as Novel Delivery Systems)，第14卷，A.C.S.学术讨论会丛刊(Symposium Series)，“药物设计中的生物可逆性载体”(Bioreversible Carriers in Drug Design)，编辑爱德华(Edward)B.罗氏(Roche)，“美国药学会”(Amer.Pharma.Assoc.)，帕加蒙出版社(Pergamon Press)(1987)，和“有机化学中的保护基团”(Protective Groups in Organic Chemistry)，麦欧米(McOmie)编辑，普莱南出版公司(Plenum Press)，纽约(1973)提供，各自通过引用以其全文结合在此。普通的酯的实例包括甲基酯、乙基酯、三氯乙基酯、丙基酯、丁基酯、戊基酯、叔丁基酯、苄基酯、硝基苄基酯、甲氧苄基酯、二苯甲基酯、甘油单酯、甘油二酯、甘油三酯。

[0085] 如在此使用的，术语“甘油单酯”是指通过酯键与甘油分子共价键合的脂肪酸链，例如DHA或EPA分子。如在此使用的，术语“甘油二酯”是指通过酯键与甘油分子共价键合的脂肪酸链，例如DHA或EPA，其中该甘油分子进一步通过一个另外的酯键与一个另外的脂肪酸链键合，该脂肪酸链可以是或可以不是DHA或EPA。如在此使用的，术语“甘油三酯”是指通过酯键与甘油分子共价键合的脂肪酸链，例如DHA或EPA，其中该甘油分子进一步通过两个另外的酯键与两个另外的脂肪酸链键合，这两个脂肪酸链的任一者或两者可以是或可以不是DHA或EPA。

[0086] 如在此使用的，术语“萜”是指由许多种植物尤其是针叶树产生的大类型且多样的有机化合物。当萜被化学修饰时，例如通过氧化或碳骨架的重排，产生的化合物通常被称为“萜类化合物”(例如，香芹酮)。萜和萜类化合物是许多类型植物和花卉的精油的主要成分。

[0087] 如在此使用的，术语“α-生育酚”、“生育酚”和“维生素E”各自是指一组生育酚

和生育三烯酚，为具有抗氧化特性的脂溶性维生素。

[0088] 如在此使用的，术语“抗氧化剂”是指能够抑制其他分子氧化的分子。氧化是从一种物质传输电子或氢到一种氧化剂上的化学反应。氧化反应可以产生自由基。进而，这些自由基可以启动链反应。当链反应在细胞中发生时，它可以引起细胞的损伤或死亡。抗氧化剂通过去除自由基中间体而终止这些链反应，并抑制其他氧化反应。它们通过自身被氧化而如此起作用，因此抗氧化剂常常是还原剂，例如硫醇、抗坏血酸、或多酚类。示例性的抗氧化剂包括迷迭香油、抗坏血酸（维生素 C）、谷胱甘肽、硫辛酸、尿酸、胡萝卜素类、褪黑激素、泛醇（辅酶 Q）、α－生育酚（维生素 E）、抗坏血酸棕榈酸酯、丁基羟基茴香醚、丁基羟基甲苯、硫代甘油、和焦亚硫酸钾。

[0089] 如在此使用的，药学上可接受的“载体”是指任何适合作为用于将分子或组合物递送到适合的体内吸收部位的媒介物的物质。这样的载体的实例包括但不限于，水、磷酸盐缓冲盐水 (PBS)、林格氏溶液、葡萄糖溶液、含血清的溶液、汉克斯溶液和其他含水的生理平衡溶液。

[0090] 如在此使用的，药学上可接受的“防腐剂”包括但不限于，山梨酸钾、尼泊金甲酯、尼泊金丙酯、苯甲酸及其盐、对羟基苯甲酸的其他酯例如尼泊金丁酯，醇类例如乙醇、苯甲醇，酚类化合物例如苯酚，或者季铵化合物例如苯扎氯铵。

[0091] 如在此使用的，“着色剂”对组合物或剂型提供了着色。这样的着色剂包括食品级染料。

[0092] 如在此使用的，术语“受试者”是指哺乳动物，包括但不限于狗、猫、马、母牛、猪、绵羊、山羊、鸡、啮齿动物、灵长类或人类。受试者包括动物，例如家庭宠物（例如，狗、猫等等）、农业牲畜受试者（例如，母牛、马、猪、鸡等等）、实验室受试者（例如，小鼠、大鼠、兔等等），但不限于此。人类受试者可以是儿科受试者、成人受试者、或者老年受试者。人类受试者可以是任一性别。

[0093] 如在此使用的，术语“心血管疾病”和“心血管病症”包括包括心脏和血管的失调，例如包括高血压、高脂血症、高甘油三酯血症、动脉粥样硬化、短暂性脑缺血发作、收缩功能障碍、舒张功能障碍、动脉瘤、主动脉夹层、心肌缺血、急性心肌梗死 (AMI)、急性 ST 段抬高型心肌梗死 (STEMI)、急性非 ST 段抬高型心肌梗死 (NSTEMI)、心绞痛、不稳定型心绞痛 (UA)、稳定型心绞痛 (SA)、心肌梗死、充血性心力衰竭、扩张性充血性心肌病、肥厚型心肌病、限制型心肌病、肺原性心脏病、心律失常、瓣膜性心脏病、心内膜炎、肺栓塞、静脉血栓形成、周围血管疾病、和外周动脉疾病。

[0094] 例如，高甘油三酯血症，是一种与心血管疾病有关的病症，其中甘油三酯的空腹血清浓度为≥ 150mg/dL。血液浓度可以从 200mg/dL 的中度高水平上升到 500mg/dL，或者在严重病例中上升到 500mg/dL 以上。美国心脏协会 (American Heart Association) 将甘油三酯浓度分类为“正常”（低于 150mg/dL）、“升高”(150 到 199mg/dL)、“高”(200 到 499mg/dL)、和“很高”(500mg/dL 以上）。对于技术从业者明显的是，高甘油三酯血症的分类可以在国家与国家之间变化。例如，加拿大和欧洲指南推荐小于 1.7mmol/L 的空腹血清甘油三酯为“令人希望的”，从 1.7 到 2.2mmol/L 为“边界高”，并且 2.3 到 5.6mmol/L 为“高”，且 5.6mmol/L 为“非常高”。技术从业者还将理解的是，构成升高的血清甘油三酯水平可以基于年龄和性别而变化。

[0095] 如在此使用的，如在一些在此的实施例中描述的“有效量”或“治疗有效量”的组合物可以是足以实现所希望的治疗作用和 / 或预防作用的量，例如，产生与正在被治疗的疾病相关联的症状的预防或减少。向受试者，尤其是需要该组合物的受试者给予的组合物的量可取决于疾病的类型和严重性并取决于个体的特征（例如整体健康状况、年龄、性别、体重和对药物的耐受性）而变化。本领域的技术人员能够根据这些和其他因素确定适当的剂型。典型地，有效量的在此描述的这些组合物可以足以实现治疗效果或预防效果。

[0096] 如在此使用的术语“剂量单位”、“单位剂量”、和“剂量单元”是指含有有效量的适合于单次给药以提供或促成治疗效果的活性成分的组合物的一部分。这样的剂量单位可以每天给予一次到多次（即，1 到大约 10，1 到 8，1 到 6，1 到 4 或 1 到 2 次），或者引出治疗反应所需要的多次。

[0097] 如在此使用的术语“食物效应”是指，当所述物质或其组合物，例如片剂、胶囊剂或液体以口服方式与食物同时或在进食状态下给予至受试者时，该活性物质的 AUC（曲线下面积）、C_{max}（最大血浆浓度）、和 / 或 T_{max}（达到最大浓度的时间）相比于在禁食状态下给予相同的组合物时的同一项值的相对差。该食物效应，F，被计算为：

[0098] $F = (Y_{进食} - Y_{禁食}) / Y_{禁食}$

[0099] 其中 $Y_{进食}$ 和 $Y_{禁食}$ 为分别在进食状态和禁食状态下的 AUC、C_{max}、或 T_{max} 的发现值。通常当 F>1 时，建立食物效应 F。

[0100] 一般而言，术语“AUC”或“血浆浓度 - 时间曲线下面积”与给予单剂量之后的体循环中可测量的活性物质的总量有关。AUC 是在给定时期中在体循环中的活性物质的聚集量的数学和视觉表示。在 AUC 方面的变化不一定必然反映被吸收的活性物质的总量的变化，但是可以反映在分布、代谢和排泄动力学方面的改变。相应地，如在此使用的术语 AUC 是指在此描述的这些组合物的单剂量给予之后在体循环中的可测量的 ω-3 脂肪酸的总量。

[0101] 术语“T_{max}”或“峰浓度时间”是指在给予单剂量之后达到血浆峰浓度所需要的时期。相应地，如在此使用的术语 T_{max} 是指给予单剂量的在此描述的任何这些组合物之后达到 ω-3 脂肪酸酯的血浆峰浓度所需要的时期。

[0102] 术语“C_{max}”或“峰浓度”是在血浆中达到的活性物质的最高浓度。相应地，如在此使用的术语 C_{max} 是指给予单剂量的在此描述的任何这些组合物之后 ω-3 脂肪酸酯的最大浓度。

[0103] 如在此使用的术语“基本上不受食物效应的影响”或“基本上没有食物效应”是指在任何在此描述的这些组合物的口服给药之后食物对吸收的影响基本消除（例如，F 大约为 0）。换言之，如通过对数转换的 AUC 所测量的这些 ω-3 脂肪酸酯的生物利用度基本上是相同的，而不论在此描述的这些组合物是与食物一起给予还是不与食物一起给予。在某些实施例中，给予在此描述的这些组合物的药理效应基本上不受食物效应的影响。

[0104] 如在此使用的术语“降低的食物效应”，如在此使用的，是指在口服给予所描述的任何这些组合物之后食物对吸收的影响的显著降低。在某些实施例中，在此描述的这些组合物具有降低的食物效应。

[0105] 如在此使用的术语“与食物同时给予”或“在进食状态下给予”是指从大约餐前 30 分钟到大约餐后 1 小时给予。

[0106] 如在此描述的医学病症的治疗或预防的各种方式旨在表示“基本的”或“基本上”，

包括总的治疗或预防，但是次于总的治疗或预防，并且，其中实现某种生物学或医学上有关的结果。需要治疗的受试者，例如人类受试者，是指需要治疗所定义的疾病状态或需要这种疾病状态的预防性治疗（即，预防）的受试者。

[0107] 如在此使用的术语“大约”或“大致”表示由本领域的普通技术人员确定的特定值在可接受的误差范围之内，这将部分地取决于该值是怎样测定或确定的，即，受到测量系统的限制。在本申请和权利要求中描述特定值的情况下，除非另外说明，术语“大约”表示该特定值在可接受的误差范围之内。

[0108] 术语“活性物质”、“活性成分”、“活性剂”或“药学活性成分”表示旨在供给药理活性或另外地在诊断、治愈、缓和、治疗或预防疾病中具有直接作用，或者在恢复、矫正或改变受试者的生理功能中具有直接作用的化学实体。

[0109] 如在此使用的术语“功能食品”表示用任何在此描述的这些组合物进行强化或增强的任何可食用的或可饮用的食品或膳食成分（例如，汁液、奶、酸奶、奶油、人造黄油、烘焙产品）。功能食品可以是，例如固体、液体、半固体，或它们的组合。术语“功能食品”还涵盖可食用和可饮用的营养补充剂。

[0110] 如在此使用的术语“亲水－亲油平衡”或“HLB”是指一种物质或组合物对于水相和油相的相对亲和力。HLB 值可以根据本领域的普通技术人员已知的方法和方程式进行计算，例如在美国专利 5,585,192 中描述的那些。物质或组合物通常具有大约 6 到大约 20 的平均 HLB。可以在提供的许多种公式或实验方法中（例如在美国专利 5,585,192 中）确定亲水－亲油平衡值。

[0111] 如在此使用的术语“基本上纯的”表示至少 90％纯的。

[0112] 药用组合物

[0113] 在至少一个实施例中，提供了一种组合物，其中该组合物包含至少一种 ω-3 脂肪酸酯、至少一种表面活性剂，并且其中当与一种水性介质接触时，该组合物自胶束化。在某些实施例中，所述至少一种 ω-3 脂肪酸酯构成从大约 40％ (wt/wt) 到大约 85％ (wt/wt) 的该组合物。在某些实施例中，该至少一种 ω-3 脂肪酸酯构成大约 40％、45％、50％、55％、60％、65％、70％、75％、80％或 85％ (wt/wt) 的该组合物。

[0114] 在某些实施例中，在此描述的这些组合物在 0.1N HCl 中自胶束化。人们公认 0.1N HCl（模拟胃液）用作胃内容物酸度的代用品。相应地，不受理论的限制，人们认为在此描述的这些组合物可以在胃或小肠中原位自胶束化。在某些实施例中，当与食物一起给予或不与食物一起给予时，在此描述的这些组合物通过肠道更高效且有效地递送 ω-3 脂肪酸酯。

[0115] 某些实施例要求使用 ω-3 脂肪酸酯。相应地，在一个方面，提供了一种组合物，该组合物包含至少一种 (5Z,8Z,11Z,14Z,17Z)－二十碳 -5,8,11,14,17- 五烯酸 (EPA) 酯；或至少一种 (4Z,7Z,10Z,13Z,16Z,19Z)－二十二碳 -4,7,10,13,16,19- 六烯酸 (DHA) 酯；或其组合，其中该组合物具有大于 2.0:1.0 到不大于 3.4:1.0 的 EPA 酯和 DHA 酯比率并且基本上不含除了所述 ω-3 脂肪酸酯以外的活性成分。在某些实施例中，在所述组合物中的这些 ω-3 脂肪酸酯包括 ω-3 脂肪酸乙酯。在某些实施例中，EPA 酯和 DHA 酯构成从至少大约 40％到大约 95％ (wt/wt) 的该组合物中的这些总 ω-3 脂肪酸酯。在某些实施例中，EPA 酯和 DHA 酯构成大约 40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、或 95％ (wt/wt) 的该组合物中的这些总 ω-3 脂肪酸酯。

[0116] 已经发现，包含具有大于2.0:1.0到不大于3.4:1.0的比率的烷基(5Z,8Z,11Z,14Z,17Z)-二十碳-5,8,11,14,17-五烯酸酯与烷基(4Z,7Z,10Z,13Z,16Z,19Z)-二十二碳-4,7,10,13,16,19-六烯酸酯(EPA:DHA)的ω-3脂肪酸酯的组合物对于降低血清中的TG浓度是有效的。在某些实施例中，EPA酯和DHA酯构成至少40％的该组合物中的这些总ω-3脂肪酸酯。在某些实施例中，EPA酯和DHA酯构成大约40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、或95％的该组合物中的这些总ω-3脂肪酸酯。还已经发现，具有包括比率大于大约2.0:1.0到不大于3.4:1.0(EPA:DHA酯)的ω-3脂肪酸酯的组合物可以被与一种或多种表面活性剂一起配制，以产生在水性介质中自胶束化的组合物。这些胶束通常呈均匀的球形并且是稳定的，保证这些ω-3脂肪酸酯的吸收基本上没有任何食物效应。根据在此描述的这些组合物在0.1N HCl中自胶束化的观察，人们认为在此描述的这些组合物也将在胃或小肠中自胶束化。在某些实施例中，这样的组合物为ω-3脂肪酸酯提供了有益的药物递送分布图。

[0117] 在某些实施例中，在此描述的包含EPA酯和DHA酯的这些组合物消除了许多常常与给予ω-3脂肪酸酯相关联的副作用。因而，在此描述的包含EPA酯和DHA酯的这些组合物没有不良气味，和/或产生令人不愉快的余味，和/或在患者中引起嗳气。在另一方面，提供了一种组合物，该组合物包含至少一种(5Z,8Z,11Z,14Z,17Z)-二十碳-5,8,11,14,17-五烯酸(EPA)酯；或至少一种(4Z,7Z,10Z,13Z,16Z,19Z)-二十二碳-4,7,10,13,16,19-六烯酸(DHA)酯；或其组合，其中该组合物具有大于大约2.0:1.0到不大于大约3.4:1.0的EPA酯和DHA酯的比率，以及至少一种表面活性剂；其中所述EPA酯、DHA酯、或其组合构成所述组合物中的ω-3脂肪酸酯的总量的至少40％。在某些实施例中，在所述组合物中的这些ω-3脂肪酸酯包括ω-3脂肪酸酯。在某些实施例中，EPA酯和DHA酯构成至少从大约40％到大约95％的该组合物中的总ω-3脂肪酸酯。相应地，在某些实施例中，EPA酯和DHA酯构成大约40％、45％、50％、55％、60％、65％、70％、75％、80％、85％、90％、或95％的该组合物中的这些总ω-3脂肪酸酯。

[0118] 在某些实施例中，EPA脂肪酸酯与DHA酯的比率是从大于2.0:1.0到不大于3.4:1.0。在某些实施例中，EPA酯与DHA酯的比率是从大约2.0:1到大约3.4:1.0。在其他实施例中，EPA酯与DHA酯的比率是从大约2.0:1.0到大约3.0:1.0。在其他实施例中，EPA酯与DHA酯的比率是从大约2.0:1.0到大约2.7:1.0。在其他实施例中，EPA酯与DHA酯的比率是从大约2.0:1.0到大约2.5:1.0。在其他实施例中，EPA酯与DHA酯的比率是从大约2.0:1.0到大约2.4:1.0。在其他实施例中，EPA酯与DHA酯的比率是从大约2.1:1.0到大约2.3:1.0。在其他实施例中，EPA酯与DHA酯的比率是从大约2.1:1.0到大约2.2:1.0。在其他实施例中，EPA酯与DHA酯的比率是大约2.4:1.0。

[0119] 在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.0:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.1:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.15:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.2:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.3:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.4:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.5:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大

约2.6:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.7:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.8:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约2.9:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约3.0:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约3.1:1.0. 在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约3.2:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约3.3:1.0。在某些实施例中，在所述组合物中EPA酯与DHA酯的所述比率是大约3.4:1.0。

[0120] 在某些实施例中，在此描述的这些组合物包含选自下述项的至少之一的ω-3脂肪酸酯：十六碳三烯酸（“HTA”或16:3(n-3)，或全顺式-7,10,13-十六碳三烯酸）、a-亚麻酸（“ALA”或18:3(n-3)，或全顺式-9,12,15-十八碳三烯酸）、十八碳四烯酸（“SDA”或18:4(n-3)或全顺式-6,9,12,15-十八碳四烯酸）、二十碳三烯酸（“ETE”或20:3(n-3)或全顺式-11,14,17-二十碳三烯酸）、二十碳四烯酸（“ETA”或20:4(n-3)、或全顺式-8,11,14,17-二十碳四烯酸）、二十碳五烯酸（“EPA”或20:5(n-3)或全顺式-5,8,11,14,17-二十碳五烯酸）、二十一碳五烯酸（“HPA”或21:5(n-3)或全顺式-6,9,12,15,18-二十一碳五烯酸）、二十二碳五烯酸（“DPA”，或鱼酸或22:5(n-3)或全顺式-7,10,13,16,19-二十二碳五烯酸）；二十二碳六烯酸（“DHA”或22:6(n-3)或全顺式-4,7,10,13,16,19-二十二碳六烯酸）、二十四碳五烯酸(24:5(n-3)或全顺式-9,12,15,18,21-二十四碳五烯酸）、二十四碳六烯酸（尼生酸或24:6(n-3)或全顺式-6,9,12,15,18,21-二十四碳六烯酸。在此处提供的某些实施例中，这些酯包括(5Z,8Z,11Z,14Z,17Z)-二十碳-5,8,11,14,17-五烯酸(EPA)的酯、(4Z,7Z,10Z,13Z,16Z,19Z)-二十二碳-4,7,10,13,16,19-六烯酸(DHA)的酯，或它们的组合。在某些实施例中，这些酯是乙酯。在某些实施例中，这些酯是单一的ω-3脂肪酸酯。在某些实施例中，这些酯是不同的ω-3脂肪酸酯的组合，例如在此叙述的那些。在某些实施例中，还可以存在其他脂肪酸或膳食油类。

[0121] 在某些实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约40％(wt/wt)的所述组合物。在某些实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约45％(wt/wt)的所述组合物。在某些实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约50％(wt/wt)的所述组合物。在其他实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约55％(wt/wt)的所述组合物。在其他实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约60％(wt/wt)的所述组合物。在其他实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约65％(wt/wt)的所述组合物。在其他实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约70％(wt/wt)的所述组合物。在其他实施例中，所述ω-3脂肪酸酯（一种或多种）构成大约75％(wt/wt)的所述组合物。在其他实施例中，该ω-3脂肪酸酯（一种或多种）构成大约80％(wt/wt)的所述组合物。在其他实施例中，该ω-3脂肪酸酯（一种或多种）构成大约85％(wt/wt)的所述组合物。在其他实施例中，该ω-3脂肪酸酯（一种或多种）构成大约90％(wt/wt)的所述组合物。在其他实施例中，该ω-3脂肪酸酯（一种或多种）构成大约95％(wt/wt)的所述组合物。

[0122] 在某些实施例中，这些组合物包括药用组合物，该药用组合物包含选自下组的第

一 ω-3 脂肪酸酯，该组的组成为：十六碳三烯酸、α－亚麻酸、十八碳四烯酸、二十碳三烯酸、二十碳五烯酸、二十一碳五烯酸、二十二碳五烯酸、二十二碳六烯酸、二十四碳五烯酸、二十四碳六烯酸的酯，或它们的组合；和选自下组的第二 ω-3 脂肪酸酯，该组的组成为：十六碳三烯酸、α－亚麻酸、十八碳四烯酸、二十碳三烯酸、二十碳五烯酸、二十一碳五烯酸、二十二碳五烯酸、二十二碳六烯酸、二十四碳五烯酸、二十四碳六烯酸的酯，或它们的组合，以及至少一种表面活性剂。有待选择的第一和第二 ω-3 脂肪酸酯将是不同的。该第一和第二 ω-3 脂肪酸酯的比率应该是从大于 2:1 到不大于 3.4:1（第一 ω-3 脂肪酸酯：第二 ω-3 脂肪酸酯）。典型地，该第一与第二 ω-3 脂肪酸酯的比率是大约 2.4:1。组合的该第一和第二 ω-3 脂肪酸酯构成从大约 40％到大约 85％ (wt/wt) 的该组合物。在某些实施例中，组合的该第一和第二 ω-3 脂肪酸酯构成至少大约 40％ (wt/wt) 的该组合物。在某些实施例中，组合的该第一和第二 ω-3 脂肪酸酯构成至少大约 45％ (wt/wt) 的该组合物。在某些实施例中，组合的该第一和第二 ω-3 脂肪酸酯构成至少大约 50％ (wt/wt) 的该组合物。在某些实施例中，组合的该第一和第二 ω-3 脂肪酸酯构成至少大约 55％ (wt/wt) 的该组合物。在某些实施例中，组合的第一和第二 ω-3 脂肪酸酯构成至少大约 60％ (wt/wt) 的该组合物。在某些实施例中，组合的该第一和第二 ω-3 脂肪酸酯构成至少大约 65％ (wt/wt) 的该组合物。在某些实施例中，组合的该第一和第二 ω-3 脂肪酸酯构成至少大约 70％ (wt/wt) 的该组合物。在某些实施例中，组合的第一和第二 ω-3 脂肪酸酯构成至少大约 75％ (wt/wt) 的该组合物。在某些实施例中，组合的第一和第二 ω-3 脂肪酸酯构成至少大约 80％ (wt/wt) 的该组合物。在某些实施例中，组合的第一和第二 ω-3 脂肪酸酯构成至少大约 85％ (wt/wt) 的该组合物。在某些实施例中，这些混合 ω-3 脂肪酸酯组合物基本上不含除了所述 ω-3 脂肪酸酯以外的活性成分。这些混合 ω-3 脂肪酸酯组合物可以进一步包含至少一种萜和 / 或至少一种抗氧化剂。该萜典型地是基本上纯的 d- 柠檬烯，并且以所述组合物的从大约 0.1％到大约 5％ (wt/wt) 的量存在。任选地，该组合物还可以进一步包含所述组合物的从大约 0.1％到大约 5％ (wt/wt) 的天然橙油。该至少一种表面活性剂可以是在此描述的这些表面活性剂的任何一种或多种，但是典型地是一种聚山梨酯和 / 或一种泊洛沙姆，例如像，聚山梨酯 80 和普朗尼克 F87。该表面活性剂以该组合物的从大约 15％到大约 31％ (wt/wt) 的量存在。该抗氧化剂（一种或多种）适合用于在这些混合的 ω-3 脂肪酸酯组合物中使用，包括但不限于生育酚类和 / 或生育三烯酚类，并且以该组合物的从大约 0.01％到大约 5％ (wt/wt) 的量存在。在某些这样的实施例中，这些生育酚和 / 或生育三烯酚可以大约按重量计这些组合物的 0.01％、0.05％、0.1％、0.2％、0.3％、0.4％、0.5％、0.6％、0.7％、0.8％、0.9％、1％、1.5％、2％、2.5％、3％、3.5％、4％、4.5％或 5％存在。在某些这样的实施例中，该抗氧化剂是一种以大约按重量计该组合物的 0.4％的量存在的生育酚。

[0123] 在某些实施例中，这些组合物包含 ω-3 脂肪酸酯，例如一种乙基酯，一种或多种表面活性剂。在某些实施例中，所述表面活性剂选自下组，该组的组成为：非离子型表面活性剂、阳离子表面活性剂、阴离子表面活性剂、两性离子表面活性剂、或它们的组合。在一些实施例中，这些组合物包括一种或多种非离子型表面活性剂。非离子型表面活性剂通常具有疏水基团和反应性氢原子，例如脂肪醇类、酸类、酰胺类和烷基酚类，带有环氧烷烃尤其是单独的环氧乙烷或者与环氧丙烷的组合。非离子型表面活性剂化合物的实例包括但不限

于聚乙二醇脱水山梨糖醇烷基酯、聚乙二醇和聚丙二醇的嵌段共聚物、乙二醇脂肪酸酯、聚（乙二醇）脂肪酸酯、脂肪酸丙二醇酯、聚（丙二醇）脂肪酸酯、乙二醇脂肪酸酯、三羟甲基丙烷脂肪酸酯、季戊四醇脂肪酸酯、葡萄糖苷衍生物、甘油烷基醚脂肪酸酯、三羟甲基丙烷氧乙烯烷基醚、脂肪酸酰胺、烷醇胺、烷基胺氧化物、羊毛脂及其衍生物、蓖麻油衍生物、硬化蓖麻油衍生物、甾醇及其衍生物、聚氧乙烯烷基醚、聚氧乙烯烷基烯丙醚、聚氧乙烯烷基胺、聚氧乙烯脂肪酰胺、聚氧乙烯烷基醇酰胺、聚氧乙烯二乙醇胺脂肪酸酯、聚氧乙烯三羟甲基丙烷脂肪酸酯、聚氧乙烯烷基醚脂肪酸酯、聚氧乙烯聚氧丙烯乙二醇、聚氧乙烯聚氧丙烯烷基醚、聚氧乙烯聚氧丙烯多元醇醚、甘油脂肪酸酯、聚甘油脂肪酸酯、聚氧乙烯甘油脂肪酸酯、脱水山梨糖醇脂肪酸酯、聚氧乙烯脱水山梨糖醇脂肪酸酯、蔗糖脂肪酸酯，或它们的组合。

[0124] 在某些实施例中，这些表面活性剂包括聚乙二醇脱水山梨糖醇烷基酯、聚乙二醇和聚丙二醇的嵌段共聚物、或它们的组合。

[0125] 聚乙二醇脱水山梨糖醇烷基酯的实例典型地是括聚山梨酯类。聚山梨酯是一类用脂肪酸酯化衍生自聚乙二醇化脱水山梨糖醇（山梨糖醇的一种衍生物）的油性液体。聚山梨酯的通用商品名包括吐温®。例如，吐温 -20、吐温 -60 和吐温 -80 可获自阿克苏诺贝尔 (AkzoNobel)（斯特拉温斯基兰 (Strawinskylaan)2555 1077 ZZ，阿姆斯特丹，荷兰）。示例性的聚山梨酯包括聚山梨酯 20（聚氧乙烯 (20) 脱水山梨糖醇单月桂酸酯）、聚山梨酯 40（聚氧乙烯 (20) 脱水山梨糖醇单棕榈酸酯）、聚山梨酯 60（聚氧乙烯 (20) 脱水山梨糖醇单硬脂酸酯）、和聚山梨酯 80（聚氧乙烯 (20) 脱水山梨糖醇单油酸酯）。

[0126] 聚乙二醇和聚丙二醇的嵌段共聚物的实例包括泊洛沙姆。泊洛沙姆是由中部疏水的聚氧丙烯（多（丙烯氧化物））链侧面连接两个亲水的聚氧乙烯（多（氧化乙烯））链构成的非离子型三嵌段共聚物。某些泊洛沙姆，例如在此列出的那些，还通过商品名普朗尼克®为人所知，其可获自供应商例如巴斯夫公司 (BASF AG（路德维希港 (Ludwigshafen)，德国）。由于聚合物嵌段的长度可以定制，存在许多不同的具有稍微不同特性的泊洛沙姆。其他示例性的普朗尼克泊洛沙姆包括但不限于：普朗尼克® 10R5、普朗尼克® 17R2、普朗尼克® 17R4、普朗尼克® 25R2、普朗尼克® 25R4、普朗尼克® 31R1、普朗尼克® F 108 浇铸固体表面活性剂 (CastSolid Surfacta)、普朗尼克® F 108NF、普朗尼克® F 108 锭剂 (Pastille)、普朗尼克® F 108 普里尔 (Prill)、普朗尼克® F 108NF 普里尔 (Prill) 泊洛沙姆 338、普朗尼克® F 127、普朗尼克® F 127 普里尔 (Prill)、普朗尼克® F 127NF、普朗尼克® F 127NF 500BHT 普里尔 (Prill)、普朗尼克® F 127NF 普里尔 (Prill) 泊洛沙姆 407、普朗尼克® F 38、普朗尼克® F38 锭剂 (Pastille)、普朗尼克® F 68、普朗尼克® F 68 锭剂 (Pastille)、普朗尼克® F 68LF 锭剂 (Pastille)、普朗尼克® F 68NF、普朗尼克® F 68NF 普里尔 (Prill) 泊洛沙姆 188、普朗尼克® F 68 普里尔 (Prill)、普朗尼克® F 68 普里尔 (Prill)、普朗尼克® F 77、普朗尼克® F 77 微锭剂 (Micropastille)、普朗尼克® F 87、普朗尼克® F 87NF、普朗尼克® F 87NF 普里尔 (Prill) 泊洛沙姆 237、普朗尼克® F 87 普里尔 (Prill)、普朗尼克® F 88、普朗尼克® F88 锭剂 (Pastille)、普朗尼克® F 88 普里尔 (Prill)、普朗尼克® F 98、普朗尼克® F 88 普里尔 (Prill)、普朗尼克® F 98、普朗尼克® F 98 普里尔 (Prill)、普朗尼克® L 10、普朗尼克® L 101、普朗尼克® L 121、普朗尼克® L 31、普朗尼克® L 35、普朗尼克® L 43、普朗尼克® L 44、普朗尼克® L 61、普朗尼克

® L 62、普朗尼克® L 62LF、普朗尼克® L 62D、普朗尼克® L 64、普朗尼克® L 81、普朗尼克® L 92、普朗尼克® L44NF INH 表面活性剂泊洛沙姆 124、普朗尼克® N 3、普朗尼克® P 103、普朗尼克® P 104、普朗尼克® P 105、普朗尼克® P123 表面活性剂、普朗尼克® P 65、普朗尼克® P 84、普朗尼克® P 85、或它们的组合。

[0127] 在某些实施例中，该组合物包含从大约 15％ (wt/wt) 到大约 31％ (wt/wt) 的聚山梨酯。在某些实施例中，所述聚山梨酯是聚山梨酯 80。在其他实施例中，该组合物包含从大约 0.5％ (wt/wt) 到大约 5％ (wt/wt) 的泊洛沙姆。在某些实施例中，该聚山梨酯是聚山梨酯 20、聚山梨酯 60、聚山梨酯 80 或其组合，并且该泊洛沙姆是普朗尼克 F 87、普朗尼克 L61、普朗尼克 F 127，或其组合。在一些实施例中，该组合物包含量为从大约 50％ (wt/wt) 到大约 80％ (wt/wt) 的 ω-3 脂肪酸酯，例如乙酯；从大约 15％ (wt/wt) 到大约 99％ (wt/wt) 的聚山梨酯；和从大约 0.05％ (wt/wt) 到大约 50％ (wt/wt) 的泊洛沙姆。在某些实施例中，该至少一种表面活性剂是所述组合物的从大约 15％ (wt/wt) 到大约 31％ (wt/wt) 的聚山梨酯例如像聚山梨酯 80、以及所述组合物的从大约 0.5％ (wt/wt) 到大约 5％ (wt/wt) 的泊洛沙姆例如像普朗尼克 F87 的组合。

[0128] 在某些实施例中，所述聚山梨酯构成大约 15％ (wt/wt) 到大约 70％ (wt/wt) 的所述组合物。在某些实施例中，所述聚山梨酯构成大约 15％ (wt/wt) 到大约 50％ (wt/wt) 的所述组合物。在某些实施例中，所述聚山梨酯构成大约 15％ (wt/wt) 到大约 31％ (wt/wt) 的所述组合物。在某些实施例中，所述聚山梨酯构成大约 15％ (wt/wt) 到大约 25％ (wt/wt) 的所述组合物。在某些实施例中，所述聚山梨酯构成大约 15％ (wt/wt) 到大约 20％ (wt/wt) 的所述组合物。在某些实施例中，所述聚山梨酯构成大约 20％ (wt/wt) 到大约 31％ (wt/wt) 的所述组合物。

[0129] 在某些实施例中，该泊洛沙姆构成从大约 0.5％ (wt/wt) 到大约 5％ (wt/wt) 的所述组合物。在某些实施例中，该泊洛沙姆构成从大约 0.5％ (wt/wt) 到大约 4％ (wt/wt) 的所述组合物。在某些实施例中，该泊洛沙姆构成从大约 0.5％ (wt/wt) 到大约 3％ (wt/wt) 的所述组合物。在某些实施例中，该泊洛沙姆构成从大约 0.5％ (wt/wt) 到大约 2％ (wt/wt) 的所述组合物。在某些实施例中，该泊洛沙姆构成从大约 0.5％ (wt/wt) 到大约 1％ (wt/wt) 的所述组合物。

[0130] 在一些实施例中，这些组合物包含一种或多种阴离子表面活性剂。示例性的“阴离子表面活性剂”包括但不限于：N- 酰基 -L- 谷氨酸二乙醇胺、N- 酰基 -L- 谷氨酸三乙醇胺、N- 酰基 -L- 谷氨酸钠、烷基磺酸钠、烷基 (C12、C14、C16) 硫酸铵、烷基 (C11、C13、C15) 硫酸三乙醇胺、烷基 (C11、C13、C15) 硫酸三乙醇胺、烷基 (C12 到 C14) 硫酸三乙醇胺、液体烷基硫酸三乙醇胺、烷基 (C12、C13) 硫酸钠、液体烷基硫酸钠、异乙二磺酸钠 (sodiumisoethionate)、乳酸 - 异硬脂酸钠 (sodium lacto-isostearate)、十一烷基烯酰氨基乙基磺基琥珀酸二钠、三乙醇胺磺基油酸盐、磺基油酸钠、油酰氨基磺基琥珀酸二钠、油酸钾、油酸钠、吗啉油酸盐、油酰肌氨酸、油酰甲基牛磺酸钠盐、含钾皂基、用于钾皂的液基、钾皂、羧基化聚氧乙烯三 (十二烷基) 醚、羧基化聚氧乙烯三 (十二烷基) 醚的钠盐 (3 环氧乙烷“E.O.”)、N- 氢化牛油脂肪酸酰基 -L- 谷氨酸三乙醇胺、N- 氢化牛油脂肪酸酰基 -L- 谷氨酸钠、氢化椰子油脂肪酸甘油硫酸钠、双十一烷基烯酰氨基乙基磺基琥珀酸钠、十八烷基硫酸钠、硬脂酸钾、三乙醇胺硬脂酸酯、硬脂酸钠、N- 硬脂酰 -L- 谷氨酸钠、硬脂

酰 L- 谷氨酸二钠、硬脂酰甲基牛磺酸钠盐、磺基琥珀酸二辛酯钠、液体磺基琥珀酸二辛酯钠、液体聚氧乙烯单油烯基氨基磺基琥珀酸二钠 (2E.O.)、聚氧乙烯月桂酰基乙醇酰胺磺基琥珀酸二钠 (5E.O.)、月桂酰基磺基琥珀酸二钠、十六烷基硫酸二乙醇胺盐、十六烷基硫酸钠、皂基、十六十八烷基硫酸钠、十三烷基硫酸三乙醇胺、棕榈酸钾、棕榈酸钠、棕榈酰甲基牛磺酸钠盐、液体蓖麻油脂肪酸钠盐 (30％)、聚氧乙烯烷基醚硫酸铵盐 (3E.O.)、液体聚氧乙烯烷基 (C12、C13) 醚硫酸二乙醇胺、液体聚氧乙烯烷基醚硫酸三乙醇胺 (3E.O.)、聚氧乙烯烷基 (C11、C13、C15) 醚硫酸三乙醇胺 (1E.O.)、聚氧乙烯烷基 (C12、C13) 醚硫酸三乙醇胺 (3E.O.)、液体聚氧乙烯烷基醚硫酸钠 (3E.O.)、聚氧乙烯烷基 (C11、C13、C15) 醚硫酸钠 (1E.O.)、聚氧乙烯烷基 (C11 到 C15) 醚硫酸钠 (3E.O.)、聚氧乙烯烷基 (C12、C13) 醚硫酸钠 (3E.O.)、聚氧乙烯烷基 (C12 到 C14) 醚硫酸钠 (3E.O.)、聚氧乙烯烷基 (C12 到 C15) 醚硫酸钠 (3E.O.)、聚氧乙烯烷基 (C12 到 C14) 磺基琥珀酸二钠 (7E.O.)、聚氧乙烯十一烷基醚硫酸钠、液体聚氧乙烯辛基苯基醚硫酸钠、聚氧乙烯油基醚硫酸铵、聚氧乙烯月桂基磺基琥珀酸二钠、聚氧乙烯壬基苯基醚硫酸钠、聚氧乙烯十五基醚硫酸钠、聚氧乙烯肉豆蔻基醚硫酸三乙醇胺、聚氧乙烯肉豆蔻基醚硫酸钠、聚氧乙烯肉豆蔻基醚硫酸钠 (3E.O.)、液体聚氧乙烯月桂基醚乙酸钠 (16E.O.)、聚氧乙烯月桂基醚硫酸铵 (2E.O.)、聚氧乙烯月桂基醚硫酸三乙醇胺、聚氧乙烯月桂基醚硫酸钠、肉豆蔻基硫酸二乙醇胺、肉豆蔻基硫酸钠、肉豆蔻基硫酸钾、N 肉豆蔻酰 -L- 谷氨酸钠、肉豆蔻酰甲基氨基乙酸钠、液体肉豆蔻酰甲基 - 丙氨酸钠盐、肉豆蔻酰甲基牛磺酸钠盐、药用皂、椰油烷基硫酸镁 / 三乙醇胺、N- 椰子油脂肪酸 - 酰基 -L- 谷氨酸三乙醇胺、N- 椰子油脂肪酸 - 酰基 -L- 谷氨酸钠、椰子油脂肪酸乙酯磺酸钠、椰子油脂肪酸钾盐、液体椰子油脂肪酸钾盐、N- 椰子油脂肪酸 / 氢化脂肪酸 - 酰基 -L- 谷氨酸钠、椰子油脂肪酸肌氨酸、椰子油脂肪酸肌氨酸三乙醇胺盐、椰子油脂肪酸肌氨酸钠盐、椰子油脂肪酸三乙醇胺盐、液体椰子油脂肪酸三乙醇胺盐、椰子油脂肪酸钠盐、椰子油脂肪酸甲基丙氨酸钠盐、液体椰子油脂肪酸甲基丙氨酸钠盐、椰子油脂肪酸甲基牛磺酸钾盐、椰子油脂肪酸甲基牛磺酸钠盐、月桂基氨基二丙酸钠、液体月桂基氨基二丙酸钠 (30％)、月桂基磺基乙酸钠 ;月桂基苯磺酸钠、月桂基硫酸盐、月桂基硫酸胺、月桂基硫酸钾、月桂基硫酸二乙醇胺、月桂基硫酸三乙醇胺、月桂基硫酸钠、月桂基硫酸镁、月桂基硫酸单乙醇胺、月桂酸钾、月桂酸三乙醇胺、液体月桂酸三乙醇胺、月桂酸钠、月桂酸 / 月桂酸三乙醇胺、月桂酰 -L- 谷氨酸三乙醇胺、N- 月桂酰 -L- 谷氨酸钠、月桂酰肌氨酸、月桂酰肌氨酸钾、液体月桂酰肌氨酸三乙醇胺盐、月桂酰肌氨酸钠、液体月桂酰甲基 - β - 丙氨酸钠盐、月桂酰甲基牛磺酸钠盐、液体月桂酰甲基牛磺酸钠盐、或它们的组合。

[0131] 在某些实施例中，所述阴离子表面活性剂 (一种或多种) 构成大约 0.05％ (wt/wt) 到大约 25％ (wt/wt) 的所述组合物。在某些实施例中，所述阴离子表面活性剂 (一种或多种) 构成大约 0.05％ (wt/wt) 到大约 15％ (wt/wt) 的所述组合物。在某些实施例中，所述阴离子表面活性剂 (一种或多种) 构成大约 0.05％ (wt/wt) 到大约 5％ (wt/wt) 的所述组合物。在某些实施例中，所述阴离子表面活性剂 (一种或多种) 构成大约 0.5％ (wt/wt) 到大约 3％ (wt/wt) 的所述组合物。在某些实施例中，所述阴离子表面活性剂 (一种或多种) 构成大约 0.7％ (wt/wt) 的所述组合物。在某些实施例中，所述阴离子表面活性剂 (一种或多种) 包括月桂基硫酸钠。

[0132] 在某些实施例中，这些组合物包含 ω-3 脂肪酸酯，例如一种乙酯，并且进一步包

含一种或多种表面活性剂。在某些实施例中，所述表面活性剂选自下组，该组的组成为：一种聚山梨酯或多种聚山梨酯的组合，以及一种阴离子表面活性剂或多种阴离子表面活性剂的组合，或者所述聚山梨酯和所述阴离子表面活性剂的组合。在其他实施例中，该组合物包含从大约 15％ (wt/wt) 到大约 31％ (wt/wt) 的聚山梨酯。在某些实施例中，所述聚山梨酯是聚山梨酯 80。在其他实施例中，该组合物包含从大约 0.5％ (wt/wt) 到大约 5％ (wt/wt) 的阴离子表面活性剂（一种或多种）。在某些实施例中，该聚山梨酯是聚山梨酯 80、聚山梨酯 20，或它们的组合，并且该阴离子表面活性剂是月桂基硫酸钠。在一些实施例中，该组合物包含量为从大约 40％ (wt/wt) 到大约 85％ (wt/wt) 的 ω-3 脂肪酸酯，例如乙酯；和从大约 15％ (wt/wt) 到大约 99％ (wt/wt) 的聚山梨酯；和从大约 0.05％ (wt/wt) 到大约 50％ (wt/wt) 的阴离子表面活性剂（一种或多种）。在一些实施例中，该组合物包含量为从大约 50％ (wt/wt) 到大约 80％ (wt/wt)(90) 的 ω-3 脂肪酸酯，例如乙酯；和从大约 15％ (wt/wt) 到大约 99％ (wt/wt) 的聚山梨酯；和从大约 0.05％ (wt/wt) 到大约 2％ (wt/wt) 的阴离子表面活性剂（一种或多种），例如像月桂基硫酸钠。在一些实施例中，该组合物包含大约 0.7％ (wt/wt) 的月桂基硫酸钠。

[0133] 在某些实施例中，所述泊洛沙姆构成大约 0.05％ (wt/wt) 到大约 25％ (wt/wt) 的所述组合物。在某些实施例中，所述泊洛沙姆构成大约 0.05％ (wt/wt) 到大约 15％ (wt/wt) 的所述组合物。在某些实施例中，所述泊洛沙姆构成大约 0.05％ (wt/wt) 到大约 5％ (wt/wt) 的所述组合物。在某些实施例中，所述泊洛沙姆构成大约 0.5％ (wt/wt) 到大约 3％ (wt/wt) 的所述组合物。

[0134] 在一些实施例中，这些组合物包含另外的表面活性剂，例如两性离子表面活性剂和阳离子表面活性剂。这样的表面活性剂的实例包括但不限于：胆汁酸（例如，胆酸、鹅去氧胆酸、甘胆酸、甘氨脱氧胆酸、牛磺胆酸、牛磺鹅脱氧胆酸、牛磺石胆酸、去氧胆酸、石胆酸、和熊去氧胆酸或它们的盐，例如，钠盐、钾盐、锂盐）、天然乳化剂（例如，阿拉伯胶、琼脂、海藻酸、海藻酸钠、黄芪胶、角叉菜 (chondrux)、胆固醇、黄原胶、果胶、明胶、蛋黄、酪蛋白、羊毛脂、胆固醇、蜡、和卵磷脂）、长链氨基酸衍生物、高分子量醇类（例如硬脂醇、鲸蜡醇、油醇、三醋精单硬脂酸酯、乙二醇二硬脂酸酯、单硬脂酸甘油酯、和丙二醇单硬脂酸酯、聚乙烯醇）、卡波姆（例如羧基聚亚甲基、聚丙烯酸、丙烯酸聚合物、和羧基乙烯基聚合物）、羧基乙烯基聚合物、纤维素衍生物（例如羧甲基纤维素钠、粉状纤维素、羟甲基纤维素、羟丙基纤维素、羟丙基甲基纤维素、甲基纤维素）、聚氧乙烯酯（例如聚氧乙烯单硬脂酸酯 [Myrj 45]、聚氧乙烯氢化蓖麻油、聚乙氧基化蓖麻油、聚氧化亚甲基硬脂酸酯 (polyoxymethylene stearate)、和聚乙二醇硬脂酸酯 (Solutol)、蔗糖脂肪酸酯、聚乙二醇脂肪酸酯（例如克列莫佛）、聚氧乙烯醚（例如聚氧乙烯月桂基醚 [Brij 30]）、聚（乙烯吡咯烷酮）、二乙二醇单月桂酸酯、三乙醇胺油酸酯、油酸钠、油酸钾、油酸乙酯、油酸、月桂酸乙酯、月桂基硫酸钠、西曲溴铵、西吡氯铵、苯扎氯铵、多库酯钠或它们的组合。

[0135] 如在此所述的适合于自胶束化的组合物通常具有从大约 12 到大约 18 的 HLB。在某些实施例中，所述组合物具有从大约 12.0 到大约 14.0 的 HLB。在某些实施例中，所述组合物具有从大约 13.0 到大约 14.0 的 HLB。在某些实施例中，所述组合物具有从大约 13.5 到大约 13.8 的 HLB。在该组合物中使用的所有这些表面活性剂或表面活化剂的总 HLB 通常是从大约 12 到大约 18。在一些实施例中，在该组合物中使用的所有表面活性剂的总 HLB

通常是从大约 12 到大约 15。在一些实施例中，在该组合物中使用的所有表面活性剂或表面活化剂的总 HLB 通常是从大约 13 到大约 15。

[0136] 在某些实施例中，该至少一种表面活性剂或表面活化剂具有至少 8.0 的 HLB。在一些实施例中，所述表面活性剂（一种或多种）或表面活化剂（一种或多种）具有在从大约 13 到大约 15 的范围内的合并 HLB。随着表面活性剂（一种或多种）或表面活化剂（一种或多种）的 HLB 值的增加，表面活性剂或表面活化剂的量需要被降低，使得 HLB 为 17 时，仅仅可能需要大约 25％ (wt/wt) 到大约 42％ (wt/wt) 的表面活性剂（一种或多种）或表面活化剂（一种或多种）。

[0137] 在某些实施例中，该组合物进一步包含一种萜。在某些实施例中，该萜是 d- 柠檬烯。在一个实施例中，该萜是一种环状萜。在一个实施例中，该萜是 d- 柠檬烯 ((+)- 柠檬烯），其为 (R)- 对映体。在一个实施例中，该萜是 L- 柠檬烯，其为 (S)- 对映体。在一个实施例中，该萜是消旋柠檬烯，称为二戊烯。在另一个实施例中，该萜是一种萜类化合物。在另一个实施例中，该萜或萜类衍生自一种天然油（例如，一种柑桔油，如橙油）。考虑了其他的萜类，例如单萜类（例如，萜品烯、萜品油烯、水芹烯、或薄荷脑），它们具有与 d- 柠檬烯相似的结构。在某些实施例中，这些组合物进一步包含按重量计该组合物的从大约 0.1％到大约 5％的基本上纯的 d- 柠檬烯。在某些其他实施例中，这些组合物进一步包含按重量计该组合物的从大约 0.1％到大约 5％的天然橙油。包含 d- 柠檬烯或橙油的组合物可以有助于将来自口服给予 ω-3 脂肪酸酯的副作用消除和 / 或降低到最低限度。这样的副作用包括反流、频繁嗳气、胃食管反流病 (GERD)、胃气胀、肠积气增加、鱼腥味道 (fish taste)、鱼腥呼吸 (fishy breath)、鱼腥气味 (fish smell)、恶心、腹泻，或它们的组合。

[0138] 在其他实施例中，该组合物进一步包含一种抗氧化剂。在某些实施例中，该抗氧化剂选自下组，该组的组成为 ：至少一种生育酚、至少一种生育三烯酚、或它们的组合。在其他实施例中，在此描述的这些组合物可以包括一种或多种生育酚。在进一步包含该至少一种或多种抗氧化剂的实施例中，该抗氧化剂（一种或多种）可以按重量计这些组合物的从大约 0.01％到大约 5％的量存在。在这样的实施例中，该抗氧化剂（一种或多种）可以大约按重量计这些组合物的 0.01％、0.05％、0.1％、0.2％、0.3％、0.4％、0.5％、0.6％、0.7％、0.8％、0.9％、1％、1.5％、2％、2.5％、3％、3.5％、4％、4.5％或 5％存在。在某些实施例中，该抗氧化剂（一种或多种）可以大约按重量计这些组合物的 0.4％的量存在。

[0139] 在至少一个另外的实施例中，提供了包含胶束的组合物，其中这些胶束是通过向一种水性介质中加入在此提供的任何一个实施例的组合物形成的，这是在将所述组合物给予至需要治疗的受试者之前进行的。可替代地，当将这些组合物添加到一种水性介质中时也可以形成胶束。在某些实施例中，这些胶束具有高达大约 10μm 的直径。在其他实施例中，基本上所有这些胶束具有从大约 1μm 到大约 10μm 的平均直径。在某些实施例中，这些胶束具有大约 1、2、3、4、5、6、7、8、9 或 10μm 的平均直径。在某些实施例中，所述胶束在室温下是稳定的。在某些实施例中，该组合物在具有酸性 pH 的水性介质中形成胶束。在某些其他实施例中，这些组合物在 0.1N HCl 中形成胶束。

[0140] 在另一个实施例中，提供了一种组合物，其中所述组合物包含至少一种 (5Z,8Z,11Z,14Z,17Z)- 二十碳 -5,8,11,14,17- 五烯酸 (EPA) 酯和至少一种 (4Z,7Z,10Z,13Z,16Z,19Z)- 二十二碳 -4,7,10,13,16,19- 六烯酸 (DHA) 酯 ；并且其中所

述组合物具有大于 2.0:1.0 到不大于大约 3.4:1.0 的 EPA 酯和 DHA 酯的比率，前提是所述 EPA 酯、DHA 酯、或其组合的浓度构成按重量计所述组合物中的 ω-3 脂肪酸酯的总量的从大约 40％到大约 85％。在某些实施例中，EPA 酯与 DHA 酯的比率是从大约 2.0:1.0 到大约 2.5:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.1:1.0 到大约 2.4:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.1:1.0 到大约 2.3:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.1:1.0 到大约 2.2:1.0。在某些实施例中，在所述组合物中的 EPA 酯与 DHA 酯的所述比率是 2.4:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.0:1.0 到大约 3.3:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.2:1.0 到大约 3.2:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.4:1.0 到大约 3.1:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.5:1.0 到大约 3.0:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.6:1.0 到大约 2.9:1.0。在其他实施例中，EPA 酯与 DHA 酯的比率是从大约 2.7:1.0 到大约 2.8:1.0。在某些实施例中，在所述组合物中 EPA 酯与 DHA 酯的所述比率大于 2.0:1.0。

[0141] 在某些实施例中，在此使用的这些 ω-3 脂肪酸酯是基本上纯的。在某些实施例中，这些 ω-3 脂肪酸酯是从大约 80％到大约 99％纯的。在某些实施例中，这些 ω-3 脂肪酸酯是至少 80％、85％、90％、92％、94％、96％、98％或 99％纯的。

[0142] 用于治疗心血管病症或失调的方法

[0143] 提供了治疗在需要治疗的受试者中的一种或多种心血管病症或失调的方法，所述方法包括向所述受试者给予治疗有效量的在此提供的任何一个实施例的组合物、或者在此提供的任何一个实施例的胶束。

[0144] 相应地，在某些实施例中，该心血管病症或失调是心脏和血管的病症或失调，例如包括高血压、高脂血症、高甘油三酯血症、动脉粥样硬化、短暂性脑缺血发作、收缩功能障碍、舒张功能障碍、动脉瘤、主动脉夹层、心肌缺血、急性心肌梗死 (AMI)、急性 ST 段抬高型心肌梗死 (STEMI)、急性非 ST 段抬高型心肌梗死 (NSTEMI)、心绞痛、不稳定型心绞痛 (UA)、稳定型心绞痛 (SA)、心肌梗死、充血性心力衰竭、扩张性充血性心肌病、肥厚型心肌病、限制型心肌病、肺原性心脏病、心律失常、瓣膜性心脏病、心内膜炎、肺栓塞、静脉血栓形成、周围血管疾病、和外周动脉疾病。

[0145] 在特定的实施例中，该心血管病症或失调是高血压、高脂血症、或它们的组合。在其他实施例中，该心血管病症或失调是高甘油三酯血症。

[0146] 在另一个实施例中，提供了用于治疗在需要治疗的受试者中的中度到重度的高甘油三酯血症的方法，其中该方法包括提供具有大约 200mg/dL 到大约 500mg/dL 的空腹基线 TG 水平的受试者，并且向该受试者给予一种如在此描述的组合物。在一个实施例中，可以从大约 0.5g 到大约 1g，从大约 1g 到大约 2g，从大约 2g 到大约 4g，从大约 4g 到大约 6g，或者从大约 6g 到大约 10g 的每日量给予该组合物。

[0147] 在某些实施例中，在该给药方案开始时具有至少 150mg/dL 的空腹血清 TG 的受试者中给予所述组合物或所述胶束的三十天之内，在该受试者的血清中的总的空腹 TG 的量降低了至少 20％。在其他实施例中，在给予所述组合物或所述胶束的三十天之内，在所述受试者的血清中的低密度脂蛋白 (LDL) 的总浓度基本上没有增加。在某些实施例中，治疗有效量的所述组合物或所述胶束包含至少 0.5g/ 天的 ω-3 脂肪酸酯。在其他实施例中，在给

予所述组合物或所述胶束之后四小时之内，所述受试者的血清具有浓度为至少 20nmol/mL 的组合的 EPA、DHA 或它们的组合。

[0148] 在另外的实施例中，提供了向受试者给予包含至少一种 ω-3 脂肪酸酯的组合物的方法，其中该受试者的血清中的高密度脂蛋白相对于 LDL 的比率是增加的。在某些实施例中，该给予为口服给予。在某些实施例中，该受试者是人。

[0149] 一些实施例提供了向受试者给予包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂的组合物的方法，其中所述至少一种 ω-3 脂肪酸酯在与一种水性介质接触时自胶束化，并且所述至少一种 ω-3 脂肪酸酯在口服给予时被所述受试者以基本上不受食物效应影响的速率吸收。在某些实施例中，食物效应的降低可以产生 F 的至少 30％、至少 40％、至少 50％、或至少 75％的降低。

[0150] 提供了一种向受试者给予包含至少一种 ω-3 脂肪酸酯和至少一种表面活性剂的组合物的方法，其中所述至少一种 ω-3 脂肪酸酯在与一种水性介质接触时自胶束化，并且所述至少一种 ω-3 脂肪酸酯在口服给予时被所述受试者以基本上不受食物效应影响的速率吸收。在某些实施例中，所述组合物是在此提供的任何一个实施例的组合物。在其他实施例中，向所述受试者给予至少 0.5g/ 天的该 ω-3 脂肪酸酯。

[0151] 在另一个实施例中，如在此描述的该组合物是例如经过大约 1 周到大约 200 周、大约 1 周到大约 100 周、大约 1 周到大约 80 周、大约 1 周到大约 50 周、大约 1 周到大约 40 周、大约 1 周到大约 20 周、大约 1 周到大约 15 周、大约 1 周到大约 12 周、大约 1 周到大约 10 周、大约 1 周到大约 5 周、大约 1 周到大约 2 周或大约 1 周的时期给予的。在另一个实施例中，如在此描述的该组合物以不受限制的时期给予至需要慢性治疗的受试者。

[0152] 在其他实施例中，在给予所述组合物之后四小时之内，所述受试者的血清具有浓度为至少 20nmol/mL 的所述至少一种 ω-3 脂肪酸酯。在其他实施例中，在给予所述组合物之后四小时之内，所述受试者的血清具有浓度为至少 50nmol/mL 的所述至少一种 ω-3 脂肪酸酯。在其他实施例中，在给予所述组合物之后四小时之内，所述受试者的血清具有浓度为至少 100nmol/mL 的所述至少一种 ω-3 脂肪酸酯。在其他实施例中，在所述受试者的血清中的所述至少一种 ω-3 脂肪酸酯的浓度可以在给予增加剂量的所述组合物之后增加。

[0153] 在某些实施例中，提供了在一种表面活性剂的存在下将由于口服给予 ω-3 脂肪酸酯所致的对需要治疗的受试者的副作用降低到最低限度和 / 或消除的方法，该方法包括给予在此提供的任何一个实施例的组合物或在此提供的任何一个实施例的胶束。在某些实施例中，将副作用降低到最低限度的方法消除了副作用的起始。在一些实施例中，这些副作用的非限制性实例包括反流、频繁嗳气、胃食管反流病 (GERD)、胃气胀、肠积气增加、鱼腥味道 (fish taste)、鱼腥呼吸 (fishy breath)、鱼腥气味 (fish smell)、恶心、腹泻，或它们的组合。

[0154] 在某些实施例中，提供了在至少一种萜或天然橙油的存在下将由于口服给予 ω-3 脂肪酸酯所致的对需要治疗的受试者的副作用降低到最低限度和 / 或消除的方法，该方法包括给予在此提供的任何一个实施例的组合物或在此提供的任何一个实施例的胶束。在某些实施例中，该至少一种萜典型地但不必需地是至少为 95％纯的 d- 柠檬烯。在某些实施例中，将副作用降低到最低限度的方法消除了副作用的起始。在一些实施例中，这些副作用的非限制性实例包括反流、频繁嗳气、胃食管反流病 (GERD)、胃气胀、肠积气增加、鱼腥味道

(fish taste)、鱼腥呼吸(fishy breath)、鱼腥气味(fish smell)、恶心、腹泻,或它们的组合。

[0155] 一些实施例提供了降低需要治疗的受试者中的食物效应的方法,该方法包括向人类受试者给予治疗有效量的任何一种在此描述的这些组合物。在某些实施例中,该食物效应基本上被消除。

[0156] 还提供了用于改进在向需要治疗的受试者口服给予 ω-3 脂肪酸酯期间的患者依从性,该方法包括给予如在此描述的组合物。

[0157] 可以向需要这样的给予的人类受试者给予在此描述的这些组合物,其中非 -ω-3 脂肪酸酯降脂剂或降胆固醇剂选自下组,该组的组成为 :胆固醇吸收抑制剂、胆汁酸螯合剂 / 树脂、他汀类药物、烟酸与衍生物、MTP 抑制剂、贝特类 (fibrates) 和 CETP 抑制剂。这些降脂剂或降胆固醇剂可以通过它们的作用机制而被分类。例如,胆固醇吸收抑制剂抑制膳食胆固醇的吸收并且抑制胆汁胆固醇的再吸收。胆固醇吸收抑制剂的实例包括但不限于植物甾醇类、依泽替米贝、和 (3R,4S)-1,4- 双 (4- 甲氧基苯基)-3-(3- 苯基丙基)-2- 氮杂环丁酮 (SCH 48461)。胆汁酸螯合剂 / 树脂为聚合化合物并用作离子交换树脂。胆汁酸螯合剂交换阴离子,例如胆汁酸的氯离子。藉此,它们结合胆汁酸并将其从肝肠循环中螯合。由于胆汁酸螯合剂是大的聚合物结构,它们并不良好地从肠吸收进入血流中。因而,胆汁酸螯合剂,连同任何与药物结合的胆汁酸在通过胃肠道之后经由粪便排泄。胆汁酸螯合剂 / 树脂的实例包括但不限于考来烯胺、考来维仑、和考来替泊。他汀类药物是抑制酶 HMG-CoA 还原酶的一类化合物。他汀类药物的实例包括但不限于罗舒伐他汀、洛伐他汀、氟伐他汀、辛伐他汀、普伐他汀、和阿托伐他汀。人们认为烟酸及其衍生物通过刺激 G 蛋白偶联受体 GPR109A 起作用,其引起脂肪组织中脂肪分解的抑制。烟酸及其衍生物的实例包括但不限于烟酸戊四醇酯、烟酸、尼可呋糖、烟酸铝、烟醇、和阿昔莫司。MTP(微粒体甘油三酯转移蛋白) 是一种脂质转移蛋白,其需要经由肝脏的极低密度脂蛋白和经由肠的乳糜微粒的装配和分泌。相应地,MTP 抑制剂降低血浆 LDL-C 的水平。MTP 抑制剂的实例包括但不限于,用于人类使用的洛美他派和用于狗的兽医用途的地洛他派和米托他派 (mitrapatide)。啮齿动物和人类研究表明,贝特类经由若干机制发挥它们的降血脂作用。贝特类的实例包括但不限于苯扎贝特、环丙贝特、氯贝丁酯、吉非贝齐、和非诺贝特。CETP(胆固醇酯转移蛋白) 抑制剂通过增加 HDL(“好的”含胆固醇颗粒) 并减少 LDL(“坏的”含胆固醇颗粒) 而改进血浆脂质谱。CETP 抑制剂的实例包括但不限于安塞曲匹 (anacetrapib) 和依塞曲匹 (evacetrapib)。

[0158] 除了前述疾病状态之外,若干其他病症或失调也可以受益于用在此描述的这些组合物治疗,例如像,代谢综合征 ;黄斑变性 (AREDS2 研究组等,年龄相关性眼病 2(AREDS2) :研究设计和基线特征 (AREDS2 报告编号 1)(The Age-Related Eye Disease 2(AREDS2):study design and baseline characteristics(AREDS2report number 1),《眼 科 学》(Opthalmology),2012 年 11 月,119(11):2282-9.doi 10.1016/j.optha 2012.05.027. 电子版 2012 年 7 月 26 ;圣乔凡尼 (SanGiovanni)JP 等人,“ω-3 长链多不饱和脂肪酸摄取和新生血管性年龄相关性黄斑变性和中央地图样萎缩的 12 年发病率 :AREDS 报告 30,一项来自年龄相关性眼病研究的前瞻性群组研究”(ω-3long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy:AREDS report 30,a

prospective cohort study from the Age-Related Eye Disease Study),《美国临床营养学杂志》(Am. J. Clin. Nutr.)2009 ;90:1601-70.) ;由于手术或外伤性脑损伤例如像,由于脑震荡导致的认知损害,(路易斯 (Lewis)M. 等人, ω-3 脂肪酸在几种头损伤中的治疗用途 (Therapeutic use of omega-3fatty acids in severe head trauma),《美国急诊医学杂志》(Am J Emerg Med.),2013年1月 ;31(1):273.e5-8.doi:10.1016/j.ajem.2012.05.014. 电子版 2012 年 8 月 3 日 ;米尔斯 (Mills)JD. 等人,"在外伤性脑损伤中的 ω-3 脂肪酸二十二碳六烯酸膳食补充"(Dietary supplementation with the omega-3fatty acid docosahexaenoic acid in traumatic brain injury),《神经外科学》(Neurosurgery)2011 年 2 月 ;68(2):474-81 ; 论 述 481.doi:10.1227/NEU.0b013e3181ff692b.) ; 重 性 抑 郁、自杀、产后抑郁 (洛根 (Logan)AC. ω-3 脂肪酸和重性抑郁 :精神卫生职业的入门书 (a primer for the mental health professional),《脂质健康疾病》(Lipids Health Dis.)2004 年 11 月,9 ;3:25 ;路易斯 (Lewis)MD 等人,"现役美国军人的自杀死亡与 ω-3 脂肪酸状态 :一项病例对照比较"(Suicide deaths of active-duty US military and omega-3fatty-acid status:a case-control comparison),《临床精神病学杂志》(J Clin Psychiatry),2011 年 12 月 ;72(12):1585-90.doi:10.4088/JCP.11m06879. 电 子 版 2011 年 8 月 23 ;马基迪斯 (Makrides)M. 等人,"二十二碳六烯酸与产后抑郁 - 存在关联吗? "(Docosahexaenoic acid and post-partum depression-is there a link?),《亚太临床营养杂志》(Asia Pac J Clin Nutr.)2003 年 ;12Suppl:S37.) ;炎症 (凯利 (Kelley)DS 等人,"DHA 补充降低高甘油三酯男性中的血清 C 反应蛋白和其他的炎症标志物"(DHA supplementation decreases serum C-reactive protein and other markers of inflammation in hypertriglyceridemic men),《营养学杂志》(J Nutr.)2009 年 3 月 ;139(3):495-501.doi:10.3945/jn.108.100354. 电 子 版 2009 年 1 月 21.) ; 原发性硬化性胆管炎 (马丁 (Martin)CR. 等人,"二十二碳六烯酸口服补充用于治疗原发性硬化性胆管炎的安全性和有效性 - 一项初步研究"(The safety and efficacy of oral docosahexaenoic acid supplementation for the treatment of primary sclerosing cholangitis-a pilot study),《消化药理学和治疗学》(Aliment Pharmacol Ther.)2012 年 1 月 ;35(2):255-65.doi:10.1111/j.1365-2036.2011.04926.x. 电子版 2011 年 11 月 30.),女性边缘型人格障碍 (扎纳里尼 (Zanarini)MC 等人,"用 ω-3 脂肪酸治疗患有边缘型人格障碍的女性 :一项双盲、安慰剂对照的初步研究"(Omega-3Fatty acid treatment of women with borderline personality disorder:a double-blind,placebo-controlled pilot study),《美国精神病学杂志》(AmJ Psychiatry),2003 年 1 月 ;160(1):167-9.),乳腺癌 (布努 (Bougnoux)P. 等人,"通过二十二碳六烯酸改善转移性乳腺癌的化疗结果 :II 期临床试验 (Improving outcome of chemotherapy of metastatic breast cancer by docosahexaenoic acid:a phase II trial),《英国癌症杂志》(Br J Cancer),2009 年 12 月 15 ;101(12):1978-85.doi:10.1038/sj.bjc.6605441. 电 子 版 2009 年 11 月 17.),非酒精性脂肪酸肝病 (帕克 (rParker)HM. 等人," ω-3 补充与非酒精性脂肪酸肝病 :一项系统综述和荟萃分析 (Omega-3supplementation and non-alcoholic fatty liver disease:a systematic review and meta-analysis),《肝脏病学杂志》(J Hepatol.),2012 年 4 月 ;56(4):944-51.doi:10.1016/j.jhep.2011.08.018. 电 子 版 2011 十 月

21；诺比利 (Nobili)V. “二十二碳六烯酸用于治疗脂肪肝：在儿童中的随机对照试验”(Docosahexaenoic acid for the treatment of fatty liver:Randomised controlled trial in children)，《营养、代谢与心血管疾病》(Nutr Metab Cardiovasc Dis.)，2012 年 12 月 7 日 .pii:S0939-4753(12)00256-6.doi:10.1016/j.numecd.2012.10.010.[印刷前电子版]；克里斯多夫 (Christopher)M.D. 等人，“鲱油降低肥胖 Ldlr-/- 小鼠中的高脂肪膳食诱导的肝损伤、脂肪变性、炎症、和纤维化的标志物”(Menhaden oil decreases high-fat diet-induced markers of hepatic damage，steatosis，inflammation，and fibrosis in obese Ldlr-/-mice)，《营养学杂志》(J Nutr.)，2012 年 8 月；142(8):1495-503.doi:10.3945/jn.112.158865. 电子版 2012 年 1 月 27.)，以及改善儿童的认知和行为（理查森 (Richardson)AJ. 等人，“二十二碳六烯酸用于改善在 7-9 岁儿童中的阅读、认知和行为：一项随机对照试验”(Docosahexaenoic acid for reading，cognition and behavior in children aged 7-9years:a randomized，controlled trial)(DOLAB 研究)，《第一科学公共图书馆》(PLoS One)2012 年；7(9):e43909.doi:10.1371/journal.pone.0043909. 电子版 2012 年 9 月 6 日）。可以通过向需要这种给药的受试者（典型地，人类）给予在此描述的这些组合物治疗来这些病症或失调。

[0159] 药盒

[0160] 在此包括包装的药用盒。这些药盒包含在一个容器中的作为单位剂型的在此描述的这些组合物和用于使用该剂型来治疗受试者的说明书，所述受试者患有响应于通过给予包含在此描述的这些组合物的剂型进行治疗的疾病或失调。

[0161] 对于例如包括但不限于受试者或医疗保健提供者，这些包装的药用盒提供了针对剂型的处方信息、非处方药医学用途、和 / 或营养信息，或提供为在包装的药用盒中的标签。包括在该药盒中的信息可以例如包括但不限于，有关 ω-3 脂肪酸剂型的功效、剂量和给药、禁忌症和副反应信息。剂量和给药信息例如可以包括给药频率以及这些组合物与食物一起或不与食物一起给予。

[0162] 在某些实施例中，包含在此提供的这些组合物的剂型处于液体或胶囊的形式，其与非处方药医学用途信息和 / 或营养信息一起提供为泡罩包装的形式或提供在瓶子中。

[0163] 包装的药用盒可以包含作为仅有的活性成分的一种或多种在此描述的这些组合物。在其他实施例中，一种或多种在此描述的这些组合物可以与一种或多种除了非 ω3 酯以外的活性成分进行组合包装，例如像，但不限于选自下组的一种或多种其他降脂剂或降胆固醇剂，该组的组成为：胆固醇吸收抑制剂、胆汁酸螯合剂 / 树脂、他汀类药物、烟酸和衍生物、MTP 抑制剂、贝特类和 CETP 抑制剂。

[0164] 剂型

[0165] 在此提供的包含至少一种 ω-3 脂肪酸酯的任何一种组合物可以被提供为药用组合物、营养保健制剂、或膳食补充剂。

[0166] 在此描述的这些药用组合物可以进一步包括一种或多种药学上可接受的赋形剂。药学上可接受的赋形剂包括但不限于载体、防腐剂、和 / 或着色剂。在药用组合物的组成和 / 或制造方面的一般考虑事项例如可见于，《雷明顿：药学技术与实践》(Remington The Science and Practice of Pharmacy)，第 21 次出版，利平科特·威廉斯·威尔金斯出版公司 (Lippincott Williams& Wilkins)，2005。

[0167] 在某些实施例中，在此描述的这些组合物可以被配制为用于口服给药的液体。液体组合物包括溶液、悬浮液和乳剂。液体药用制剂的实例包括丙二醇溶液和含有用于口服溶液的甜味剂的溶液、悬浮液和乳剂。当液体组合物与一种水性介质例如像具有酸性环境的水性介质接触时，该组合物形成胶束。

[0168] 在某些实施例中，该剂型包含在向需要这样的给予的受试者给予之前预先形成的胶束。这样的预先形成的胶束在室温下是稳定的。

[0169] 在其他实施例中，在此描述的这些组合物可以被配制为用于软胶囊的填充材料。同样，当该软胶囊的内容物与一种水性介质接触时，该组合物在该胶囊崩解后形成胶束。

[0170] 可以例如通过将以上描述的这些组合物置于胶囊壳内部来制备一种胶囊。胶囊是一种以含有活性剂的特殊容器或外壳给予的剂型。在一些实施例中，在此描述的这些组合物可以填充到软胶囊中。胶囊壳可以由甲基纤维素、羟丙基甲基纤维素、聚乙烯醇、或变性明胶或淀粉或其他材料制成。硬壳胶囊典型地由具有较高凝胶强度的骨明胶和猪皮明胶的混合物制成。在一些实施例中，该单位剂型是凝胶胶囊。在一些实施例中，该胶囊壳是甘油胶囊壳，例如产品号 GSU0051，其由瑞士软胶囊公司 (swisscaps) 制造并且符合 USP 25 要求 (瑞士软胶囊公司，美国 14193SW 119 大道，迈阿密 / 佛罗里达州 (Miami/Fla.)，美国 33186)。在其他实施例中，该胶囊是一种牛明胶壳，例如瑞士软胶囊公司 (swisscaps) 的产品号 GSU0708。其他适合的胶囊壳材料包括聚乙烯、聚丙烯、聚 (甲基丙烯酸甲酯)、聚氯乙烯、聚苯乙烯、聚氨酯类、聚四氟乙烯、尼龙、聚甲醛、聚酯类、乙酸纤维素、和硝酸纤维素。胶囊壳自身可以含有小量的染料、遮光剂 (opaquing agent)、增塑剂、和防腐剂。用于制备其他固体剂型例如胶囊、栓剂等等的常规方法也是众所周知的。明胶胶囊壳也可以由木薯淀粉、草、蔬菜衍生的或者鱼类衍生的明胶制成。例如 K-CAPS(凯普修林公司 (Capsuline, Inc.)，庞帕诺比奇 (Pompano Beach)，佛罗里达) 是一种合乎标准的蔬菜来源的按犹太教规供应的 (Kosher) 软胶囊壳。其他素食来源的明胶胶囊可以由蔬菜来源的羟丙基甲基纤维素 (HPMC) 制成。胶囊壳也可以含有改性的玉米淀粉、甘油、和角叉菜胶作为胶凝剂。

[0171] 在其他实施例中，胶囊具有包含限速膜材料的壳，包括包衣材料，并且填充有在此描述的这些组合物。胶囊壳可以由多孔的或者 pH 敏感的聚合物经由一个热成形工艺制成。在某些实施例中，胶囊壳处于非对称膜的形式；即，一种在一个表面上具有薄皮而其大部分的厚度由高渗透性多孔材料构成的膜。

[0172] 然而可以使用另一种有用的胶囊，一种“胀塞装置”(“swelling plug device”)。在此描述的这些组合物可以结合到该装置的非溶性胶囊半部分中，该装置可以在一端被水凝胶塞密封。这种水凝胶塞在水性环境中溶胀，并且，在溶胀持续预定的时间之后退出该胶囊，因而打开一个活性剂可以从其离开该胶囊并且被递送到该水性环境中的孔口。优选的水凝胶塞胶囊为展现出基本上没有活性剂从该剂型中释放的胶囊，直到该剂型已经离开胃并已留在小肠中持续大约 15 分钟或更久 (优选地大约 30 分钟或更久) 时为止，从而保证最少的 ω-3 脂肪酸酯被释放到胃或小肠中。这种类型的水凝胶塞胶囊已经描述于专利申请 WO 90/19168 中。

[0173] 这些剂型可以含有增塑剂，尤其是在胶囊壳中。适合的增塑剂包括，例如，聚乙二醇类，如 PEG 300、PEG 400、PEG 600、PEG 1450、PEG 3350、和 PEG 800、硬脂酸、丙二醇、油酸、三乙基纤维素、三醋精、甘油、山梨醇、脱水山梨糖醇或它们的组合。

[0174] 在另外的实施例中，这些组合物可以被配制为用于肠胃外给药的液体。

[0175] 组合物可以被配制为一个或多个剂量单位。在一些实施例中，可有利的是配制处于剂量单位形式的口服组合物，以便易于给药并且剂量一致。描述在一些实施例中的单位剂量形式可以是指适合于作为针对有待治疗的受试者的单一剂量的物理离散单位；每一单位包含预定量的活性组合物，该预定量经计算与适合的药用载体结合以产生所希望的治疗效果。在某些实施例中，该剂型可任选地含有调味剂，例如橙油、基本上纯的 d- 柠檬烯、和一种抗氧化剂如生育酚、抗坏血酸棕榈酸酯或抗氧化剂的组合。

[0176] 功能食品

[0177] 在某些实施例中，在此描述的这些组合物包含在向需要这样的给予的受试者给予之前预先形成的胶束。这样的预先形成的胶束在室温下是稳定的。

[0178] 相应地，可以将在此描述的这样的预先形成的胶束或预先胶束化的组合物添加到食物中，然后，这些食物可作为用于富集受试者的 ω-3 脂肪酸水平的健康膳食的一部分而被消费，或者作为除了如由健康专业人员开处方的在此描述的这些组合物的口服 / 肠胃外给药之外的膳食治疗。

[0179] 在某些实施例中，该功能食品处于可食用或可饮用的组合物的形式，例如，诸如可咀嚼或可食用条、糖果产品（例如，巧克力条）、曲奇、汁饮料、烘焙或模拟烘焙商品（例如，布朗尼）、饼干、脆性硬糖或口香糖之类的食品。可咀嚼或可食用条的实例包括巧克力条或能量棒。这样的功能食品对于参加运动或其他形式的练习的人们可以是特别有用的。

[0180] 在某些实施例中，这些功能食品可可以处于例如奶油、人造黄油、面包、蛋糕、奶昔、冰淇淋、酸奶和其他发酵奶制品的形式。

[0181] 在某些实施例中，该功能食品也可以处于有待被喷雾到肉类、沙拉或其他食品上的液体的形式。

[0182] 这些功能食品的其他形式可以是早餐谷物，例如像谷物片、木斯里 (muesli)、麦麸、燕麦片。

[0183] 当该功能食品处于可饮用形式时，在此描述的这些组合物可以被直接添加到饮料中，例如像原味牛奶、风味奶、发酵奶制品或汁液。这些组合物将在该可饮用产品中形成包含 ω-3 脂肪酸酯的胶束。

[0184] 当该功能食品处于固态可食用产品的形式时，在此描述的这些组合物可以首先被添加到一种水性介质中，其中该组合物将形成如在此所述的胶束。然后该包含胶束的水性介质可以被喷雾到固态可食用产品上或者在制造该可食用产品时混合到这些成分中。

[0185] 本发明进一步通过参考以下实例进行限定，这些实例并不旨在限制本发明的范围。本领域的技术人员将清楚的是，可以对材料和方法两者实施许多修改，而不偏离本发明的目的和意义。

[0186] 非限制性工作实例

[0187] 实例 1

[0188] 构成该组合物的这些成分的量和百分比显示在表 1 中：

[0189] 表 1

[0190]

组合物（填充物质）/剂型		
成分	量（mg）	%（wt/wt）
总 ω-3 脂肪酸乙酯	754.3	68.57
- EPA 乙酯	392.2	35.65
- DHA 乙酯	165.9	15.08
聚山梨酯 80	337.9	30.72
普朗尼克 F87	7.8	0.71

[0191]

凝胶块/剂型		
成分	量（gm）	%（wt/wt）
明胶	270	40
甘油	135	20
纯净水	270	40

[0192] 包含一个实施例的该组合物的剂型的制造过程可以分成三个阶段：a）制造该组合物（填充物质）的过程，b）制造用于包封该填充物质的凝胶块的过程，以及 c）包封过程。阶段（a）和（b）可以按照任一顺序进行。

[0193] 通过根据所希望的批量大小称取适量的聚山梨酯 80 和普朗尼克 F87 并且将它们在 60℃在一个不锈钢罐中混合均匀，开始制造该组合物的过程。在基本上纯的 ω-3 脂肪酸乙酯混合物定量地真空转移到含有聚山梨酯 80 和普朗尼克 F87 的相同的不锈钢罐中之前，使这种混合物冷却到室温。在用氮气覆盖之前，将这种混合物再次在室温下混合均匀。这个最终的组合物也被称为“填充物质”。

[0194] 通过根据所希望的批量大小称取各自适量的甘油和水，并且将它们在大约 80℃在分开的不锈钢混合器中混合均匀，开始制造该凝胶块的过程。其次，根据该批量大小称取适量的明胶，添加到该甘油 / 水混合物中，并且在真空下除气之前，再次在 80℃混合均匀。包含甘油 / 水 / 明胶的这个最终混合物被称为“凝胶块”。

[0195] 取决于所希望的胶囊形状，将适合的模具和转移管安装在软凝胶包封设备中（由 SKY 软胶囊有限公司（SKY Softgel Co.Ltd.）提供的 SS-60 软胶囊机（Softgel Encapsulation Machine），仁川，韩国）。将填充物质泵入含有包含该半固体凝胶块的预先成型的带状物的模具中。用模具将这些软胶囊成形，然后将这些软胶囊滚筒干燥大约 20-60 分钟。将这些胶囊转移到盘上，并且在低温 / 湿度的干燥室中干燥，并干燥直到这些胶囊达到 75 以上的肖氏硬度。然后，将这些胶囊检视、分选、抛光、印花并包装到瓶子中。将这些

瓶子附上标签，该标签包括处方信息。可替代地，将这些瓶子包装到盒子中，这些盒子带有包括处方信息的包装说明书。

[0196] 实例 2

[0197] 进行实验来确定两种组合物 A 和 B 中的胶束信息，如在表 2 中所示。如在实例 1 中所述制备包含 ω-3 脂肪酸乙酯的两种组合物，其中这些 ω-3 脂肪酸乙酯具有增加的吸收，并且该食物效应被基本消除。

[0198] 表 2

[0199]

成分	% (wt/wt)	
	组合物 A	组合物 B
ω-3 脂肪酸乙酯	68.57	75.0
聚山梨酯 80，NF	30.71	20.0
普朗尼克 F87	0.71	5.0

[0200]

组合表面活性剂 HLB	15.3	16.8
完整产品 HLB	13	13.2

[0201] 形成良好分散的胶束的这些组合物通常具有大约 15 到大约 17 的组合表面活性剂 HLB 值。

[0202] 具有与大约 7％到大约 22％之间的普朗尼克 F87 组合的 27％ -29％之间的聚山梨酯 80 水平的其他组合物通常形成大的油球。这些组合物具有从大约 17 到大约 19 的组合表面活性剂 HLB 值。基于这些实验，完整产品的 HLB 为从大约 13 到大约 14.4，并且该组合表面活性剂 HLB 在 12 到大约 17 之间。

[0203] 实例 3

[0204] 在美国药典 (USP) 溶出度 2 条件下，如描述于美国药典的 34/ 国家处方集 /2011 的通则 711 中，将如在表 2 中所示的组合物 A 和 B(1,000mg) 添加到分开的含有 0.1N HCl 中的 500-900mL 水的容器中，并观察。两种组合物都不经受任何搅拌或剪切。当在显微镜下观察时，可见非常小的、良好分散的胶束。这些胶束在室温下经过十二个月是稳定的，并且 ω-3 脂肪酸酯没有明显地从该组合物的其他成分分离。因而，包含与 0.7％到 5％的普朗尼克 F87 组合的在 20％ -31％之间的聚山梨酯 80 水平的组合物形成了稳定的胶束。

[0205] 实例 4

[0206] 人类受试者摄入实例 2 中的组合物 A(该“实验组合物”) 并经历血液监测，以便测量相比于代表当前市售的药物和营养 ω-3 产品 (“标准组合物”) 的 ω-3 脂肪酸乙酯组合物中的 ω-3 脂肪酸乙酯，ω-3 脂肪酸乙酯吸收的增加。通过使用标准包封方法包封 ω-3 乙酯制造了该标准组合物。通过比较摄入这些组合物之后在受试者中的 ω 指数的变化，确

定了 ω-3 脂肪酸乙酯的吸收，正如使用由 ωQuant 提供的 ω 指数试剂盒测定的。在摄入组合物之前，从受试者抽血来确定受试者的基线 ω 指数。然后受试者摄入含有该实验组合物或者该标准组合物的软胶囊。在摄入四小时之后进行后续的抽血。从该初始基线抽血开始到该四小时抽血期间，使该受试者保持该禁食状态。结果显示在表 4 中。

[0207] 表 4

[0208]

胶囊组合物	剂量	ω 指数		
	EPA + DHA 乙酯	初始	4 小时	增加
标准组合物	1.52 g	5.2	5.3	1.92%
实验组合物 -剂量 A （4 个胶囊，每个胶囊 400 mg 总填充重量）	1.46 g	5.4	5.7	5.55%

[0209]

实验组合物 -剂量 B （10 个胶囊，每个胶囊 400 mg 总填充重量）	3.65 g	4.9	5.3	8.16%

[0210] 实例 5

[0211] 进行了开放标签的随机化的 3 组平行组概念验证性研究，以便评估在空腹条件下给药时的 SC401 胶囊 1100mg（如在实例 1 中所述制造的）对LOVAZA® （ω-3- 酸乙酯）胶囊 1000mg 对安慰剂在具有 250 与 500mg/dL 之间的血清 TG 的高甘油三酯受试者中的血清 TG 降低效果和安全性。

[0212] 这项研究的目标在于评估 SC401 对LOVAZA®对安慰剂在 14 天治疗期间对 TG 降低的效果。45 位受试者纳入该项研究中，以便在三个治疗组中每组具有完备的至少 12 位受试者。

[0213] 以下纳入和排除标准用来选择用于本研究的受试者：

[0214] 纳入标准：

[0215] • 18 岁或以上的男性和女性；

[0216] • 血清 TG 在 200 与 500mg/dL 之间。

[0217] • 根据病史、简要体格检查、心电图、和常规实验室试验正常有活力且健康。

[0218] • 对于他的 / 她的身高而言，根据所附的身高 / 体重表值（参见所附身高 / 体重表），既不是过重，也不是体重不足。

[0219] • 提供书面的知情同意书。

[0220] • 如果是女性并具有怀孕可能；在该研究期间实施可接受的由研究者判断的生育控制方法，例如避孕套、泡沫、凝胶剂、隔膜、宫内节育器 (IUD)、或禁欲；或为绝经后至少 1 年；或进行了手术绝育（两侧输卵管结扎、双侧卵巢切除、或子宫切除）。

[0221] 排除标准：

[0222] • 重度高甘油三酯血症（血清 TG>500mg/dL）。

[0223] • 对 ω-3 或鱼油不耐受。

[0224] • 在研究药物初始给予三个月之内或者在该研究期间使用了 ω-3 鱼油、其他 EPA 或 DHA 和 / 或 DHA 强化的食品或其他降 TG 药物。

[0225] • 在研究药物初始给予七天之内或者在该研究期间消费了任何鱼油。

[0226] • 最近有某些心脏、肾脏、肝脏、肺、或胃肠道疾病或癌症（除了非黑色素瘤皮肤癌之外）病史。

[0227] • 糖尿病或在接受胰岛素治疗。

[0228] • 怀孕或哺乳的女性。没有使用医学上认可的避孕方法的具有怀孕可能的女性。

[0229] • 使用了某些类型的激素、抗惊厥药、免疫性药物、抗生素、抗真菌药和抗病毒药、以及心脏药物。

[0230] • 使用了华法林（香豆素）。

[0231] • 最近（过去 12 个月）有药物滥用或酒精滥用史。

[0232] • 在研究药物给予之前 28 天之内暴露于任何研究产品。

[0233] • 经诊断患有下列病症的受试者：

[0234] • 内分泌性糖尿病、甲状腺机能减退、妊娠；

[0235] • 营养性肥胖、酒精使用；

[0236] • 肾脏肾变病、慢性肾衰竭；

[0237] • 肝病胆汁郁积、肝细胞功能障碍；

[0238] • 免疫球蛋白过量性副蛋白血症 (Immunoglobulin excess paraproteinemia)；

[0239] • 痛风；

[0240] • 研究者认为将干扰患者提供知情同意书、顺从研究指令的能力、或者可能混淆研究结果的解释或将患者置于不适当的风险的任何其他情况；以及正在应用下列药物的受试者：噻嗪类利尿剂、类固醇激素、微粒体酶类、视黄酸衍生物、蛋白酶抑制剂 (HIV 感染)。

[0241] 知情同意书 (ICD) 由志愿者在研究特异性程序之前阅读并签字。另外，对每一个时期的临床项目进行了下列试验

[0242] • 药物滥用的尿筛查 - 包括可卡因、印度大麻、苯丙胺类、巴比妥类、苯二氮卓类和阿片类。如果对于这些药物的结果为阳性，受试者从该研究淘汰 / 撤出，

[0243] • 酒精呼吸试验 - 如果对于酒精的结果为阳性，受试者从该研究淘汰 / 撤出，

[0244] • 尿妊娠试验 (HCG)（仅仅对于女性受试者而言）- 如果对于妊娠的结果为阳性，女性受试者从该研究淘汰 / 撤出，以及

[0245] • 妇科 & 乳腺检查（仅仅对于女性受试者而言）- 如果在检查中有任何异常，受试

者从该研究淘汰 / 撤出。

[0246] 受试者从给药前至少 48 小时到至少 14 天收容在临床设施中并且要求在该设施中停留连续 16 个夜晚。

[0247] 受试者在给药上午之前至少 10 个小时禁食，并且至少在给药之前 48 小时并且在整个研究过程中被命令避开消费咖啡因和 / 或含有黄嘌呤的产品（即，咖啡、茶、巧克力、和含有咖啡因的苏打水、可乐，等等）、酒精与维生素补充剂，包括维生素 C 和抗坏血酸以及葡萄柚和其果汁。在该研究过程中没有提供柑桔汁，包括橙汁和葡萄柚汁。

[0248] 在 10 小时的过夜禁食之后，受试者在如下的单色光或低光条件下给药：

[0249] 在觉醒时（在早餐之前至少 2 个小时仅仅用水服用到排空的胃中）服用 SC401（ω-3 脂肪酸乙酯，1100mg）2 个胶囊（为单剂量），然后在就寝前（在晚餐之后至少 2 个小时仅仅用水服用，并且此后在夜间不摄入食物或液体）服用 2 个胶囊（为单剂量），或者

[0250] 在觉醒时（在早餐之前至少 2 个小时仅仅用水服用到排空的胃中）服用 LOVAZA®（ω-3 脂肪酸乙酯，1000mg，葛兰素史克公司 (GlaxoSmithKline)，RTP，NC 2770）2 个胶囊（为单剂量），然后在就寝前（在晚餐之后至少 2 个小时仅仅用水服用，并且此后在夜间不摄入食物或液体）服用 2 个胶囊（为单剂量），或者

[0251] 在觉醒时（在早餐之前至少 2 个小时仅仅用水服用到排空的胃中）服用安慰剂（油酸乙酯，1000mg 胶囊）2 个胶囊（为单剂量），然后在就寝前（在晚餐之后至少 2 个小时仅仅用水服用，并且此后在夜间不摄入食物或液体）服用 2 个胶囊（为单剂量）。

[0252] 包含 Lovaza、SC401 和该安慰剂的 ω-3 脂肪酸乙酯的量显示在表 5 中：

[0253] 表 5

[0254]

胶囊填充组合物（mg）	SC401	Lovaza®	安慰剂
总 ω-3 脂肪酸乙酯	754.3	934	0
- EPA 乙酯	392.2	482	0
- DHA 乙酯	165.9	370	0
聚山梨酯 80，NF	337.9	0	0

[0255]

普朗尼克 F87	7.8	0	0
油酸乙酯	0	0	1000

[0256] 在研究期间收集 4 个血液样品（每个 8mL）。将在 T_s、T_0、T_{7d}、T_{14d} 处通过直接静脉

穿刺将血液样品收集在普通真空管中。将真空采血管竖立放置在保持在湿的冰浴中的支架中，直到转移到诊断科室时为止。

[0257] 对于 T_s、T_0、T_{7d}、T_{14d}，测定了在三个组中的每一个组的每位患者的空腹甘油三酯 / HDL/LDL/ 总胆固醇 / 非 -HDL/ 水平。

[0258] 数据列表于以下表 6 中：

[0259] 表 6

[0260]

	在距离基线*14 天处的结果		
	SC401	Lovaza®	安慰剂
血清甘油三酯水平	-48.5%	-29.4%	-27.7%
*SC401 结果被调节成与 Lovaza®组中给予的总 EPA 乙酯和 DHA 乙酯的量匹配。			

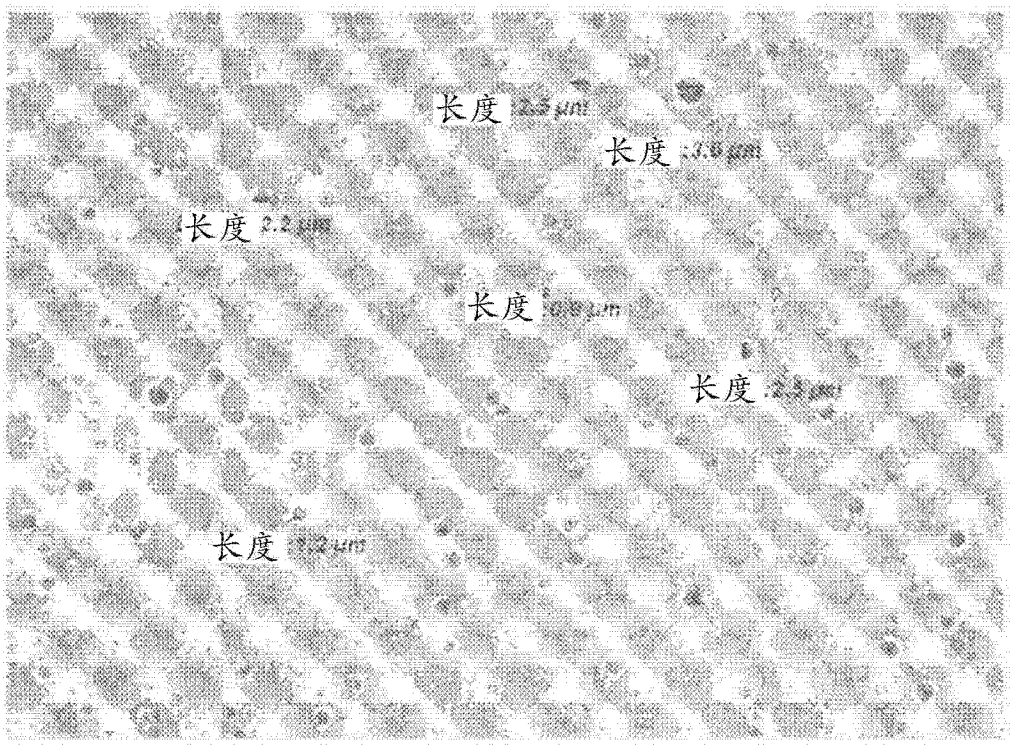


图 1

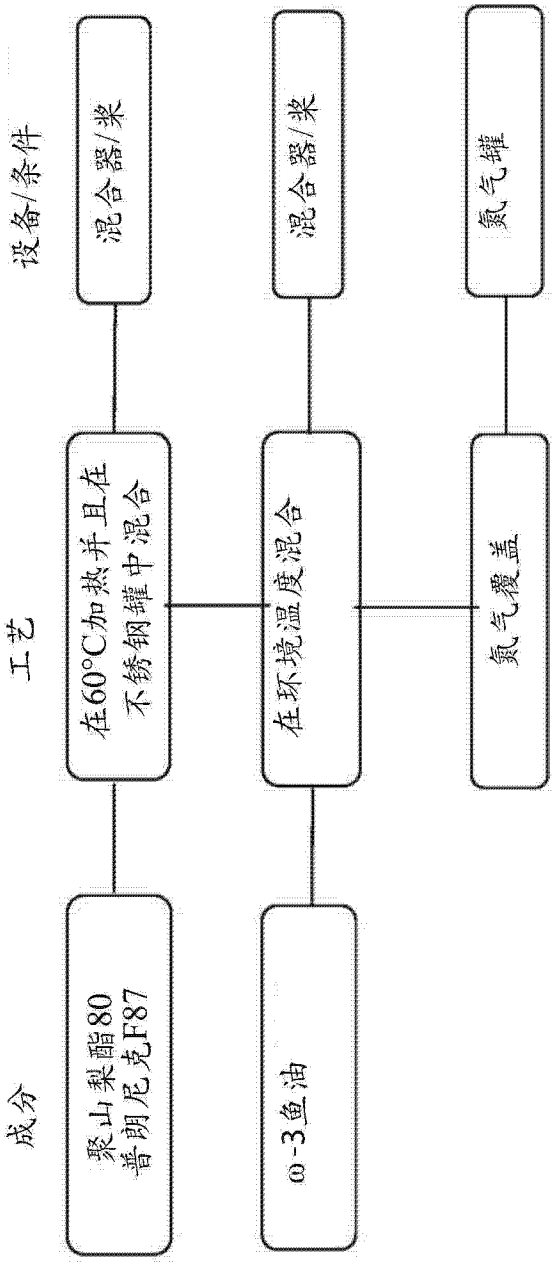

设备/条件
混合器/浆
混合器/浆
氮气罐
工艺
在60°C加热并且在不锈钢罐中混合
在环境温度混合
氮气覆盖
成分
聚山梨酯80
普朗尼克F87
ω-3鱼油

图 2

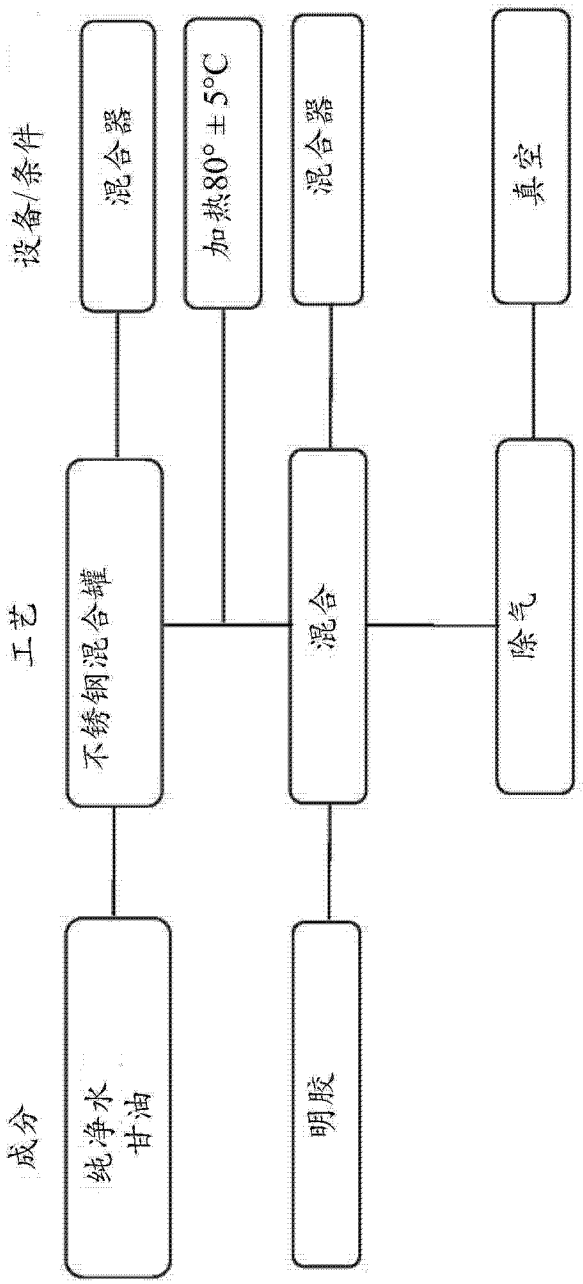

设备/条件
混合器
加热80° ± 5°C
混合器
真空
工艺
不锈钢混合罐
混合
除气
成分
纯净水
甘油
明胶

图 3

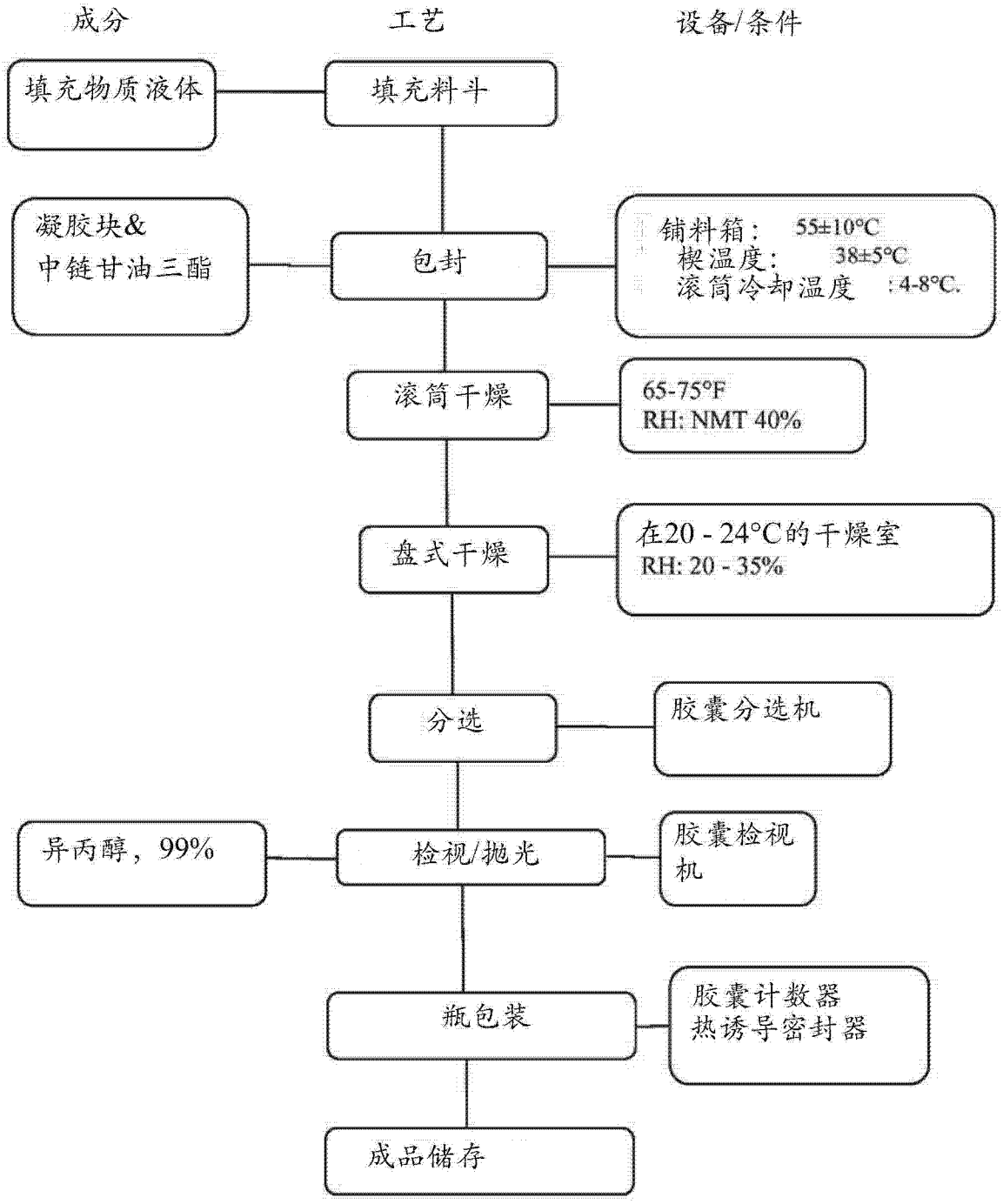

成分
工艺
设备/条件
填充物质液体
填充料斗
凝胶块&
中链甘油三酯
包封
铺料箱： 55±10°C
楔温度： 38±5°C
滚筒冷却温度 :4-8°C.
滚筒干燥
65-75°F
RH: NMT 40%
盘式干燥
在20 - 24°C的干燥室
RH: 20 - 35%
分选
胶囊分选机
异丙醇，99%
检视/抛光
胶囊检视
机
瓶包装
胶囊计数器
热诱导密封器
成品储存

图 4

Abstract

Described herein are compositions comprising at least one Omega-3 fatty acid ester and at least one surface active agent; wherein the compositions form micelles when in contact with an aqueous medium. Also provided is a method of administering to a subject a composition comprising at least one Omega-3 fatty acid ester and at least one surface active agent, wherein the at least one Omega-3 fatty acid ester forms micelles when in contact with an aqueous medium, and the bioavailability of the at least one Omega-3 fatty acid ester is substantially independent of a food effect. Said compositions are useful for treating cardiovascular conditions or disorders in a subject and for reducing side effects associated with the ingestion of Omega-3 fatty acid esters. Described are also various dosage forms for administering said compositions and use of said compositions in functional foods. Provided herein are also kits with instructions on how to administer said compositions.