(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 October 2010 (21.10.2010)

PCT

(10) International Publication Number
WO 2010/119319 A1

(51) International Patent Classification:
A61K 9/66 (2006.01) *A61K 9/08* (2006.01)
A61K 31/202 (2006.01) *A61K 9/107* (2006.01)
A61K 31/557 (2006.01) *A61K 9/20* (2006.01)

(21) International Application Number:
PCT/IB2010/000788

(22) International Filing Date:
9 March 2010 (09.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/158,613 9 March 2009 (09.03.2009) US
61/242,630 15 September 2009 (15.09.2009) US
61/254,291 23 October 2009 (23.10.2009) US
61/254,293 23 October 2009 (23.10.2009) US

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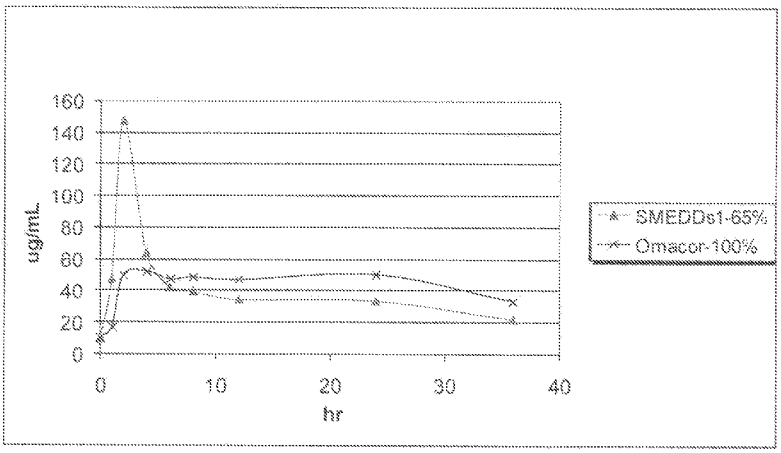
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: COMPOSITIONS COMPRISING A FATTY ACID OIL MIXTURE AND A FREE FATTY ACID, AND METHODS AND USES THEREOF

FIG. 37



(57) **Abstract**: Compositions comprising a fatty acid oil mixture and at least one free fatty acid, and uses thereof are disclosed. Further disclosed are preconcentrates capable of forming a self- nanoemulsifying drug delivery system (SNEDDS), a self-microemulsifying drug delivery system (SMEDDS) or self-emulsifying drug delivery systems (SEDDS) in an aqueous solution. Preferred fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in a form chosen from ethyl ester and triglyceride.

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COMPOSITIONS COMPRISING A FATTY ACID OIL MIXTURE AND A FREE FATTY ACID, AND METHODS AND USES THEREOF

[001] This application claims priority to U.S. Provisional Application No. 61/158,613, filed on March 9, 2009, U.S. Provisional Application No. 61/242,630, filed on September 15, 2009, U.S. Provisional Application No. 61/254,291, filed on October 23, 2009, and U.S. Provisional Application No. 61/254,293, filed on October 23, 2009, all of which are incorporated herein by reference in their entireties.

[002] The present disclosure relates generally to compositions comprising a fatty acid oil mixture and at least one free fatty acid, and methods of use thereof. The fatty acid oil mixture may comprise omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in ethyl ester or triglyceride form. Further disclosed are preconcentrate compositions and self-nanoemulsifying drug delivery systems (SNEDDS), self-microemulsifying drug delivery systems (SMEDDS) and self-emulsifying drug delivery systems (SEDDS).

[003] The compositions presently disclosed may be administered, e.g., in capsule or tablet form, to a subject for therapeutic treatment and/or regulation of at least one health problem including, for example, irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, hypertriglyceridemia, heart failure, and post myocardial infarction (MI). The present disclosure further relates to a method of increasing hydrolysis, solubility, bioavailability, absorption, and/or any combination thereof.

[004] In humans, cholesterol and triglycerides are part of lipoprotein complexes in the bloodstream and can be separated via ultracentrifugation into high-density lipoprotein (HDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) fractions. Cholesterol and triglycerides are synthesized in the liver, incorporated into VLDL, and released into the plasma. High levels of total cholesterol (total-C), LDL-C, and apolipoprotein B (a membrane complex for LDL-C and VLDL-C) promote human atherosclerosis and decreased levels of HDL-C and its transport complex; apolipoprotein A is also associated with the development of atherosclerosis. Furthermore, cardiovascular morbidity and mortality in humans can vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. In addition, research suggests that non-HDL cholesterol is an indicator of hypertriglyceridemia, vascular disease, atherosclerotic disease, and related conditions. In fact, NCEP ATP III specifies non-HDL cholesterol reduction as a treatment objective.

[005] Omega-3 fatty acids may regulate plasma lipid levels, cardiovascular and immune functions, insulin action, and neuronal development, and visual function. Marine

oils, also commonly referred to as fish oils, are a source of omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been found to regulate lipid metabolism. Plant-based oils and microbial oils are also sources of omega-3 fatty acids. Omega-3 fatty acids may have beneficial effects on the risk factors for cardiovascular diseases, for example hypertension and hypertriglyceridemia, and on the coagulation factor VII phospholipid complex activity. Omega-3 fatty acids may also lower serum triglycerides, increase serum HDL cholesterol, lower systolic and diastolic blood pressure and/or pulse rate, and may lower the activity of the blood coagulation factor VII-phospholipid complex. Further, omega-3 fatty acids are generally well-tolerated, without giving rise to severe side effects.

[006] Several formulations of omega-3 fatty acids have been developed. For example, one form of omega-3 fatty acid oil mixture is a concentrate of primary omega-3, long chain, polyunsaturated fatty acids from fish oil containing DHA and EPA, such as sold under the trademark Omacor® / Lovaza™ / Zodin® / Seacor®. See, for example, U.S. Patent Nos. 5,502,077, 5,656,667 and 5,698,594. In particular, each 1000 mg capsule of Lovaza™ contains at least 90% omega-3 ethyl ester fatty acids (84% EPA/DHA); approximately 465 mg EPA ethyl ester and approximately 375 mg DHA ethyl ester.

[007] Further, for example, EPA/DHA ethyl esters have also been used in compositions for delivery of therapeutic drugs. For instance, U.S. Patent No. 6,284,268 (Cyclosporine Therapeutics Ltd.) describes a self-emulsifying microemulsion or emulsion preconcentrate pharmaceutical compositions containing an omega-3 fatty acid oil and poorly water soluble therapeutic agent such as cyclosporine for oral administration. Cyclosporines are claimed to have additive or synergistic therapeutic effects with omega-3 fatty acid oil. The '268 patent discloses greater solubility and stability of cyclosporine formulations comprising omega-3 fatty acid oils. WO 99/29300 (RTP Pharma) relates to self-emulsifying fenofibrate formulations based on a hydrophobic component selected from triglyceride, diglyceride, monoglycerides, free fatty acids and fatty acids and derivatives thereof.

[008] However, evidence suggests that long chain fatty acids and alcohols of up to at least C_{24} are reversibly interconverted. Enzyme systems exist in the liver, fibroblasts, and the brain that convert fatty alcohols to fatty acids. In some tissues, fatty acids can be reduced back to alcohols. The carboxylic acid functional group of fatty acid molecules targets binding, but this ionizable group may hinder the molecule from crossing the cell membranes, such as of the intestinal wall. As a result, carboxylic acid functional groups are often protected as esters. The ester is less polar than the carboxylic acid, and may more easily cross the fatty cell membranes. Once in the bloodstream, the ester can

be hydrolyzed back to the free carboxylic acid by enzyme esterase in the blood. It may be possible that the plasma enzymes do not hydrolyze the ester fast enough, however, and that the conversion of ester to free carboxylic acid predominantly takes place in the liver. Ethyl esters of polyunsaturated fatty can also be hydrolyzed to free carboxylic acids in vivo.

[009] Thus, there remains a need in the art for compositions and/or methods that improve or enhance solubilization, digestion, bioavailability and/or absorption of omega-3 fatty acids in vivo, while maintaining the ability to cross cell membranes.

[010] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the present disclosure, as claimed.

[011] The present disclosure is directed to a pharmaceutical composition comprising: a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid.

[012] The present disclosure is also directed to a pharmaceutical preconcentrate comprising: a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant.

[013] For example, the present disclosure provides for a pharmaceutical preconcentrate comprising: a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; at least one free fatty acid comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the at least one free fatty acid, wherein the EPA and DHA are in free fatty acid form; and at least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof.

[014] Further for example, the present disclosure provides for a pharmaceutical preconcentrate comprising: from about 45% to about 55% by weight, relative to the weight of the preconcentrate, of a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; from about 5% to about 15% of at least one free fatty acid, by weight relative to the weight of the preconcentrate; and from about 30% to about 40% of at least one surfactant, by weight relative to the weight of the preconcentrate.

[015] The present disclosure is also directed to a pharmaceutical preconcentrate comprising: from about 55% to about 65% by weight, relative to the weight of the preconcentrate, of a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; from about 5% to about 15% of at least one free fatty acid, by weight relative to the weight of the preconcentrate; and from about 20% to about 30% of at least one surfactant, by weight relative to the weight of the preconcentrate.

[016] The present disclosure is yet still further directed to a pharmaceutical preconcentrate comprising: a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; at least one free fatty acid comprising oleic acid; and at least one surfactant chosen from polysorbate 20 and polysorbate 80.

[017] The present disclosure is also directed to a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) comprising a pharmaceutical preconcentrate comprising: a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant; wherein the preconcentrate forms an emulsion in an aqueous solution.

[018] The present disclosure further provides for a method of treating at least one health problem in a subject in need thereof comprising administering to the subject a pharmaceutical composition comprising: a pharmaceutically-effective amount of a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid; wherein the at least one health problem is chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction. For example, the composition further comprises at least one surfactant to form a pharmaceutical preconcentrate, such as, the preconcentrate forms a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) in an aqueous solution.

[019] In addition, the present disclosure is directed to a food supplement or nutritional supplement composition comprising: a fatty acid oil mixture comprising from

about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid. For example, the composition further comprises at least one surfactant to form a supplement preconcentrate, such as the preconcentrate forms a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) in an aqueous solution.

[020] The present disclosure is also directed to a method for enhancing at least one parameter chosen from hydrolysis, solubility, bioavailability, absorption, and combinations thereof of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) comprising combining: a fatty acid oil mixture comprising EPA and DHA in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid. For example, a method for enhancing at least one parameter chosen from hydrolysis, solubility, bioavailability, absorption, and combinations thereof of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) comprising combining: a fatty acid oil mixture comprising EPA and DHA in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant; wherein the fatty acid oil mixture, that at least one free fatty acid, and the at least one surfactant form a preconcentrate. In addition, the preconcentrate forms a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) in an aqueous solution.

[021] In a further embodiment, the present disclosure is directed to a pharmaceutical composition comprising a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid for the treatment of at least one health problem chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

[022] In yet still a further embodiment, the present disclosure provides for a pharmaceutical preconcentrate comprising a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant for the treatment of at least one health problem chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

[023] The present disclosure is also directed to a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) comprising a pharmaceutical preconcentrate comprising: a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant; wherein the preconcentrate forms an emulsion in an aqueous solution for the treatment of at least one health problem chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

[024] The present disclosure is further directed to a method of regulating at least one health problem in a subject in need thereof comprising administering to the subject a supplement composition comprising: a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid; wherein the at least one health problem is chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

[025] The present disclosure is also further directed to a method of regulating at least one health problem in a subject in need thereof comprising administering to the subject a supplement composition comprising: a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant; wherein the at least one health problem is chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

[026] The present disclosure is yet still further directed to a food supplement or nutritional supplement composition comprising: a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid for the regulation of at least one health problem chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

[027] The present disclosure is also further directed to a food supplement or nutritional supplement preconcentrate comprising: a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant for the regulation of at least one health problem chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

BRIEF DESCRIPTION OF THE DRAWINGS

[028] FIG 1 shows the viscosity of preconcentrates A-L.

[029] FIG 2 shows the average particle size distribution for preconcentrates A-F, I, and J in gastric media and intestinal media.

[030] FIG 3 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate A in gastric media.

[031] FIG 4 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate B in gastric media.

[032] FIG 5 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate C in gastric media.

[033] FIG 6 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate D in gastric media.

[034] FIG 7 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate E in gastric media.

[035] FIG 8 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate F in gastric media.

[036] FIG 9 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate I in gastric media.

[037] FIG 10 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate J in gastric media.

[038] FIG 11 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate A in intestinal media.

[039] FIG 12 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate B in intestinal media.

[040] FIG 13 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate C in intestinal media.

[041] FIG 14 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate D in intestinal media.

[042] FIG 15 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate E in intestinal media.

[043] FIG 16 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate F in intestinal media.

[044] FIG 17 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate I in intestinal media.

[045] FIG 18 shows the read out from the Malvern zetasizer for four consecutive measurements on preconcentrate J in intestinal media.

[046] FIG 19 shows the disappearance of EPA-EE and DHA-EE and the appearance of EPA-FA and DHA-FA during lipolysis of Omacor® .

[047] FIG 20 shows the percent recovery of EPA + DHA at different time-points for Omacor®.

[048] FIG 21 shows the percent lipolysis of EPA-EE, DHA-EE and total K85EE at different time points for Omacor®.

[049] FIG 22 shows the disappearance of EPA-EE and DHA-EE and the appearance of EPA-FA and DHA-FA during lipolysis of preconcentrate A.

[050] FIG 23 shows the percent recovery of EPA + DHA at different time-points for preconcentrate A.

[051] FIG 24 shows the percent lipolysis of EPA-EE, DHA-EE and total K85EE at different time points for preconcentrate A.

[052] FIG 25 shows the disappearance of EPA-EE and DHA-EE and the appearance of EPA-FA and DHA-FA during lipolysis of preconcentrate B.

[053] FIG 26 shows the percent recovery of EPA + DHA at different time-points for preconcentrate B.

[054] FIG 27 shows the percent lipolysis of EPA-EE, DHA-EE and total K85EE at different time points for preconcentrate B.

[055] FIG 28 shows the disappearance of EPA-EE and DHA-EE and the appearance of EPA-FA and DHA-FA during lipolysis of preconcentrate C.

[056] FIG 29 shows the percent recovery of EPA + DHA at different time-points for preconcentrate C.

[057] FIG 30 shows the percent lipolysis of EPA-EE, DHA-EE and total K85EE at different time points for preconcentrate C.

[058] FIG 31 shows the disappearance of EPA-EE and DHA-EE and the appearance of EPA-FA and DHA-FA during lipolysis of preconcentrate D.

[059] FIG 32 shows the percent recovery of EPA + DHA at different time-points for preconcentrate D.

[060] FIG 33 shows the percent lipolysis of EPA-EE, DHA-EE and total K85EE at different time points for preconcentrate D.

[061] FIG 34 shows the disappearance of EPA-EE and DHA-EE and the appearance of EPA-FA and DHA-FA during lipolysis of preconcentrate E.

[062] FIG 35 shows the percent recovery of EPA + DHA at different time-points for preconcentrate E.

[063] FIG 36 shows the percent lipolysis of EPA-EE, DHA-EE and total K85EE at different time points for preconcentrate E.

[064] FIG 37 shows the plasma concentration versus time profile of the total lipid concentration of EPA for Example 14.

DESCRIPTION

[065] Particular aspects of the disclosure are described in greater detail below. The terms and definitions as used in the present application and as clarified herein are intended to represent the meaning within the present disclosure. The patent and scientific literature referred to herein and referenced above is hereby incorporated by reference. The terms and definitions provided herein control, if in conflict with terms and/or definitions incorporated by reference.

[066] The singular forms "a," "an," and "the" include plural reference unless the context dictates otherwise.

[067] The terms "approximately" and "about" mean to be nearly the same as a referenced number or value. As used herein, the terms "approximately" and "about" should be generally understood to encompass ± 10% of a specified amount, frequency or value.

[068] The terms "administer," "administration" or "administering" as used herein refer to (1) providing, giving, dosing and/or prescribing by either a health practitioner or his authorized agent or under his direction a composition according to the disclosure, and (2) putting into, taking or consuming by the patient or person himself or herself, a composition according to the disclosure.

[069] The present disclosure provides for pharmaceutical and supplement compositions comprising a fatty acid oil mixture and at least one free fatty acid, and methods of use thereof. The compositions can further comprise at least one surfactant to form a preconcentrate. The preconcentrates of the present disclosure can produce dispersions of low or very low mean particle size when mixed with an aqueous medium. Such dispersions can be characterized as nanoemulsions, microemulsions, or emulsions. For example, upon delivery, the preconcentrates are thought to produce dispersions with gastric or other physiological fluids generating self-nanoemulsifying drug delivery systems

(SNEDDS), self-microemulsifying drug delivery systems (SMEDDS), or self emulsifying drug delivery systems (SEDDS).

Fatty acid oil mixture

[070] Compositions of the present disclosure comprise at least one fatty acid oil mixture. The fatty acid oil mixture comprises eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). As used herein, the term "fatty acid oil mixture" includes fatty acids, such as unsaturated (e.g., monounsaturated, polyunsaturated) or saturated fatty acids, as well as pharmaceutically-acceptable esters, free acids, mono-, di- and triglycerides, derivatives, conjugates, precursors, salts, and mixtures thereof. In at least one embodiment, the fatty acid oil mixture comprises fatty acids, such as omega-3 fatty acids, in a form chosen from ethyl ester and triglyceride.

[071] The term "omega-3 fatty acids" includes natural and synthetic omega-3 fatty acids, as well as pharmaceutically-acceptable esters, free acids, triglycerides, derivatives, conjugates (see, e.g., Zaloga et al., U.S. Patent Application Publication No. 2004/0254357, and Horrobin et al., U.S. Patent No. 6,245,811, each hereby incorporated by reference), precursors, salts, and mixtures thereof. Examples of omega-3 fatty acid oils include, but are not limited to, omega-3 polyunsaturated, long-chain fatty acids such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), α-linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), and octadecatetraenoic acid (i.e., stearidonic acid, STA); esters of omega-3 fatty acids with glycerol such as mono-, di- and triglycerides; and esters of the omega-3 fatty acids and a primary, secondary and/or tertiary alcohol, such as, for example, fatty acid methyl esters and fatty acid ethyl esters. The omega-3 fatty acids, esters, triglycerides, derivatives, conjugates, precursors, salts and/or mixtures thereof according to the present disclosure can be used in their pure form and/or as a component of an oil, for example, as marine oil (e.g., fish oil and purified fish oil concentrates), algae oils, microbial oils and plant-based oils.

[072] In some embodiments of the present disclosure, the fatty acid oil mixture comprises EPA and DHA. Further for example, the fatty acid oil mixture comprises EPA and DHA in a form chosen from ethyl ester and triglyceride.

[073] The fatty acid oil mixture of the present disclosure may further comprise at least one fatty acid other than EPA and DHA. Examples of such fatty acids include, but are not limited to, omega-3 fatty acids other than EPA and DHA and omega-6 fatty acids. For example, in some embodiments of the present disclosure, the fatty acid oil mixture comprises at least one fatty acid other than EPA and DHA chosen from α-linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), and stearidonic acid (STA). In some embodiments,

the at least one fatty acid other than EPA and DHA is chosen from linoleic acid, gamma-linolenic acid (GLA), arachidonic acid (AA), docosapentaenoic acid (i.e., osbond acid), and mixtures thereof. In some embodiments, the at least one fatty acid other than EPA and DHA is in a form chosen from ethyl ester and triglyceride.

[074] Examples of further fatty acids, or mixtures thereof (fatty acid oil mixtures) encompassed by the present disclosure include, but are not limited to, the fatty acids defined in the European Pharamacopoeia Omega-3 Ethyl Esters 90 and purified marine oils, for example, the European Pharamacopoeia Omega-3 Acid Triglycerides, the European Pharamacopoeia Omega-3 acid Ethyl Esters 60, the European Pharmacopoeia Fish Oil Rich in Omega-3 Acids monograph, and/or for instance, the USP fish oil monograph.

[075] Commercial examples of fatty acid oil mixtures comprising different fatty acids suitable for the present disclosure include, but are not limited to: Incromega™ omega-3 marine oil concentrates such as Incromega™ TG7010 SR, Incromega™ E7010 SR, Incromega™ TG6015, Incromega™ EPA500TG SR, Incromega™ E400200 SR, Incromega™ E4010, Incromega™ DHA700TG SR, Incromega™ DHA700E SR, Incromega™ DHA500TG SR, Incromega™ TG3322 SR, Incromega™ E3322 SR, Incromega™ TG3322, Incromega™ E3322, Incromega™ Trio TG/EE (Croda International PLC, Yorkshire, England); EPAX6000FA, EPAX5000TG, EPAX4510TG, EPAX2050TG, EPAX7010EE, EPAX5500EE, EPAX5500TG, EPAX5000EE, EPAX5000TG, EPAX6000EE, EPAX6000TG, EPAX6000FA, EPAX6500EE, EPAX6500TG, EPAX4510TG, EPAX1050TG, EPAX2050TG, EPAX 7010TG, EPAX7010EE, EPAX6015TG/EE, EPAX4020TG, and EPAX4020EE (EPAX is a wholly-owned subsidiary of Norwegian company Austevoll Seafood ASA); Omacor® / Lovaza™ / Zodin® / Seacor® finished pharmaceutical product, K85EE, and AGP 103 (Pronova BioPharma Norge AS); MEG-3® EPA/DHA fish oil concentrates (Ocean Nutrition Canada); DHA FNO "Functional Nutritional Oil" and DHA CL "Clear Liquid" (Lonza); Superba™ Krill Oil (Aker); omega-3 products comprising DHA produced by Martek; Neptune krill oil (Neptune); cod-liver oil products and anti-reflux fish oil concentrate (TG) produced by Møllers; Lysi Omega-3 Fish oil; Seven Seas Triomega® Cod Liver Oil Blend (Seven Seas); Fri Flyt Omega-3 (Vesterålens); and Epadel (Mochida). Those commercial embodiments provide for various omega-3 fatty acids, combinations, and other components as a result of the transesterification process or method of preparation in order to obtain the omega-3 fatty acid(s) from various sources, such as marine, algae, microbial, and plant-based sources.

[076] In some embodiments of the present disclosure, the fatty acid oil mixture comprises at least one fatty acid derivative, such as an alpha-substituted omega-3 fatty

acid derivative. The at least one alpha substituted omega-3 fatty acid derivative may be substituted, for example, at the second carbon atom from the functional group of the omega-3 fatty acid with at least one substituent chosen from hydrogen, hydroxyl groups, alkyl groups, such as C_1-C_3 alkyl groups, and alkoxy groups. In one embodiment of the present disclosure, the at least one alpha-substituted omega-3 fatty acid derivative is chosen from mono-substituted and di-substituted fatty acids. In one embodiment, the at least one alpha substituted omega-3 fatty acid derivative is chosen from alpha-substituted C_{14}-C_{24} alkenes having 2 to 6 double bonds. In another embodiment, the at least one alpha-substituted omega-3 fatty acid derivative is chosen from alpha-substituted C_{14}-C_{24} alkenes having 5 or 6 double bonds in cis configuration.

[077] In some embodiments, the fatty acid oil mixture comprises EPA and/or DHA in a form of an alpha-substituted fatty acid derivative. For example, in one embodiment, the fatty acid oil mixture comprises EPA in a form of an alpha-substituted derivative. In another embodiment, the fatty acid oil mixture comprises DHA in a form of an alpha-substituted derivative. In yet another embodiment, the fatty acid oil mixture comprises EPA and DHA in a form of an alpha-substituted derivative.

[078] In some embodiments, the fatty acid oil mixture comprises EPA and DHA, and further comprises at least one alpha-substituted omega-3 fatty acid derivative. For example, in some embodiments, the fatty acid oil mixture comprises EPA and DHA, and at least one of EPA and DHA in a form of an alpha-substituted derivative.

[079] In another embodiment, the EPA and DHA of the fatty acid oil mixture is at least one alpha-substituted omega-3 fatty acid derivative.

[080] The fatty acid oil mixture according to the present disclosure may be derived from animal oils and/or non-animal oils. In some embodiments of the present disclosure, the fatty acid oil mixture is derived from at least one oil chosen from marine oil, algae oil, plant-based oil, and microbial oil. Marine oils include, for example, fish oil, krill oil, and lipid composition derived from fish. Plant-based oils include, for example, flaxseed oil, canola oil, mustard seed oil, and soybean oil. Microbial oils include, for example, products by Martek. In at least one embodiment of the present disclosure, the fatty acid oil mixture is derived from a marine oil, such as a fish oil. In at least one embodiment, the marine oil is a purified fish oil.

[081] In some embodiments of the present disclosure, the fatty acids, such as omega-3 fatty acids, of the fatty acid oil mixture are esterified, such as alkyl esters and further for example, ethyl ester. In other embodiments, the fatty acids are chosen from mono-, di-, and triglycerides.

[082] In some embodiments, the fatty acid oil mixture is obtained by a transesterification of the body oil of a fat fish species coming from, for example, anchovy

or tuna oil, and subsequent physico-chemical purification processes, including urea fractionation followed by molecular distillation. In some embodiments, the crude oil mixture may also be subjected to a stripping process for decreasing the amount of environmental pollutants and/or cholesterol before the transesterification.

[083] In another embodiment, the fatty acid oil mixture is obtained by using supercritical CO_2 extraction or chromatography techniques, for example to up-concentrate primary EPA and DHA from fish oil concentrates.

[084] In some embodiments of the present disclosure, at least one of the omega-3 fatty acids of the fatty acid oil mixture has a cis configuration. Examples include, but are not limited to, (all-Z)-9,12,15-octadecatrienoic acid (ALA), (all-Z)-6,9,12,15-octadecatetraenoic acid (STA), (all-Z)-11,14,17-eicosatrienoic acid (ETE), (all-Z)-5,8,11,14,17-eicosapentaenoic acid (EPA), (all-Z)-4,7,10,13,16,19-docosahexaenoic acid (DHA), (all-Z)-8,11,14,17-eicosatetraenoic acid (ETA), (all-Z)-7,10,13,16,19-docosapentaenoic acid (DPA), (all-Z)-6,9,12,15,19-heneicosapentaenoic acid (HPA); (all-Z)-5,8,11,14-eicosatetraenoic acid, (all-Z)-4,7,10,13,16-docosapentaenoic acid (osbond acid), (all-Z)-9,12-octadecadienoic acid (linoleic acid), (all-Z)-5,8,11,14-eicosatetraenoic acid (AA), (all-Z)-6,9,12-octadecatrienoic acid (GLA); (Z)-9-octadecenoic acid (oleic acid), 13(Z)-docosenoic acid (erucic acid), (R-(Z))-12-hydroxy-9-octadecenoic acid (ricinoleic acid).

[085] In some embodiments of the present disclosure, the weight ratio of EPA:DHA of the fatty acid oil mixture ranges from about 1:10 to about 10:1, from about 1:8 to about 8:1, from about 1:6 to about 6:1, from about 1:5 to about 5:1, from about 1:4 to about 4:1, from about 1:3 to about 3:1, or from about 1:2 to 2 about :1. In at least one embodiment, the weight ratio of EPA:DHA of the fatty acid oil mixture ranges from about 1:2 to about 2:1. In at least one embodiment, the weight ratio of EPA:DHA of the fatty acid oil mixture ranges from about 1:1 to about 2:1. In at least one embodiment, the weight ratio of EPA:DHA of the fatty acid oil mixture ranges from about 1.2 to about 1.3.

Free fatty acid (FFA)

[086] The compositions presently disclosed comprise at least one free fatty acid. Without being bound by theory, it is believed that the addition of at least one free fatty acid may enhance or improve lipolysis of the fatty acid oil mixture in the body, e.g., the interconversion of fatty acid esters and/or triglycerides to the free fatty acid form for efficient uptake. The addition of at least one free fatty acid may, for example, provide for enhanced or improved hydrolysis, solubility, bioavailability, absorption, or any combinations thereof of fatty acids of the fatty acid oil mixture in vivo.

[087] Examples of free fatty acids include, but are not limited to, EPA, DHA, α-linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA),

eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), stearidonic acid (STA), linoleic acid, gamma-linolenic acid (GLA), arachidonic acid (AA), osbond acid, oleic acid, ricinoleic acid, erucic acid, and mixtures thereof. In at least one embodiment, the at least one free fatty acid is a polyunsaturated fatty acid.

[088] In some embodiments, the at least one free fatty acid is chosen from oleic acid, ricinoleic acid, linoleic acid, and erucic acid. In one embodiment, the at least one free fatty acid comprises oleic acid or linoleic acid.

[089] In some embodiments, the at least one free fatty acid comprises at least 80% omega-3 fatty acids by weight of the at least one free fatty acid, such as at least 90% omega-3 fatty acids by weight of the at least one free fatty acid.

[090] In some embodiments, the at least one free fatty acid comprises at least 75% EPA and DHA by weight of the at least one free fatty acid. For example, in some embodiments, the at least one free fatty acid comprises at least 80% by weight, at least 85% by weight, at least 90% by weight, or at least 95% EPA and DHA, by weight of the at least one free fatty acid. In some embodiments, the at least one free fatty acid comprises about 80% EPA and DHA by weight of the at least one free fatty acid, such as about 85%, about 90%, about 95%, or any number in between, by weight of the at least one free fatty acid. The at least one free fatty acid can be used in a pure form and/or as a component of an oil, for example, as marine oil (e.g., fish oil and purified fish oil concentrates), microbial oil and plant-based oils.

[091] In some embodiments, the at least one free fatty acid comprises from about 75% to about 95% EPA and DHA by weight of the at least one free fatty acid, such as from about 75% to about 90%, from about 75% to about 85%, from about 75% to about 80%, from about 80% to about 95%, from about 80% to about 90%, from about 80% to about 85%, from about 85% to about 95%, from about 85% to about 90%, and further for example, from about 90% to about 95% by weight of the at least one free fatty acid, or any number in between. In at least one embodiment, the at least one free fatty acid comprises from about 80% to about 85% EPA and DHA, by weight of the at least one free fatty acid, such as from about 80% to about 88% EPA and DHA by weight, such as about 84%, by weight of the at least one free fatty acid.

[092] Commercial embodiments of at least one free fatty acid encompassed by the present disclosure include, but are not limited to, K85FA (Pronova BioPharma Norge AS).

Pharmaceutical

[093] In some embodiments of the present disclosure, the fatty acid oil mixture acts as an active pharmaceutical ingredient (API). For example, the present disclosure provides for a pharmaceutical composition comprising a fatty acid oil mixture and at least

one free fatty acid. In some embodiments, the fatty acid oil mixture is present in a pharmaceutically-acceptable amount. As used herein, the term "pharmaceutically-effective amount" means an amount sufficient to treat, e.g., reduce and/or alleviate the effects, symptoms, etc., at least one health problem in a subject in need thereof. In at least some embodiments of the present disclosure, the fatty acid oil mixture does not comprise an additional active agent.

[094] Where the composition is a pharmaceutical composition, the fatty acid oil mixture comprises at least 75% EPA and DHA by weight of the fatty acid oil mixture. For example, in one embodiment, the fatty acid oil mixture comprises at least 80% EPA and DHA by weight of the fatty acid oil mixture, such as at least 85%, at least 90%, or at least 95%, by weight of the fatty acid oil mixture. In some embodiments, the fatty acid oil mixture comprises about 80% EPA and DHA by weight of the fatty acid oil mixture, such as about 85%, about 90%, about 95%, or any number in between, by weight of the fatty acid oil mixture.

[095] For example, in some embodiments, the fatty acid oil mixture comprises from about 75% to about 95% EPA and DHA by weight of the fatty acid oil mixture, such as from about 75% to about 90%, from about 75% to about 88%, from about 75% to about 85%, from about 75% to about 80%, from about 80% to about 95%, from about 80% to about 90%, from about 80% to about 85%, from about 85% to about 95%, from about 85% to about 90%, and further for example, from about 90% to about 95% EPA and DHA, by weight of the fatty acid oil mixture, or any number in between. In at least one embodiment, the fatty acid oil mixture comprises from about 80% to about 85% EPA and DHA, by weight of the fatty acid oil mixture, such as from about 80% to about 88%, such as about 84%, by weight of the fatty acid oil mixture.

[096] In some embodiments, the fatty acid oil mixture comprises at least 95% of EPA or DHA, or EPA and DHA, by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form.

[097] In a further embodiment, the fatty acid oil mixture may comprise other omega-3 fatty acids. For example, the present disclosure encompasses at least 90% omega-3 fatty acids, by weight of the fatty acid oil mixture.

[098] In one embodiment, for example, the fatty acid oil mixture comprises from about 75% to about 88% EPA and DHA, by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; wherein the fatty acid oil mixture comprises at least 90% of omega-3 fatty acids in ethyl ester form, by weight of the fatty acid oil mixture.

[099] In another embodiment, the fatty acid oil mixture comprises from about 75% to about 88% EPA and DHA, by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; wherein the fatty acid oil mixture comprises at least 90%

of omega-3 fatty acids in ethyl ester form, by weight of the fatty acid oil mixture, and wherein the fatty acid oil mixture comprises α-linolenic acid (ALA).

[0100] In one embodiment, the fatty acid oil mixture comprises from about 80% to about 88% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form, and further comprises docosapentaenoic acid (DPA) in ethyl ester form.

[0101] In another embodiment, the fatty acid oil mixture comprises from about 80% to about 88% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form, and further comprises from about 1% to about 4% (all-Z omega-3)-6,9,12,15,18-heneicosapentaenoic acid (HPA) in ethyl ester form, by weight of the fatty acid oil mixture.

[0102] In another embodiment, the fatty acid oil mixture comprises from about 80% to about 88% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; and from 1% to about 4% fatty acid ethyl esters other than EPA and DHA, by weight of the fatty acid oil mixture, wherein the fatty acid ethyl esters other than EPA and DHA have C_{20}, C_{21}, or C_{22} carbon atoms.

[0103] In one embodiment, the fatty acid oil mixture may comprise K85EE or AGP 103 (Pronova BioPharma Norge AS). In another embodiment, the fatty acid oil mixture may comprise K85TG (Pronova BioPharma Norge AS).

[0104] In one embodiment, the pharmaceutical composition comprising at least K85EE, K85-FA, and Tween 20 or 80, for example, provide for enhanced bioavailability. For example, the bioavailability may be increased > about 40%, such as, about 80%.

EPA and DHA products

[0105] In at least one embodiment, the fatty acid oil mixture comprises at least 75% EPA and DHA by weight of the fatty acid oil mixture, of which at least 95% is EPA. In another embodiment, the fatty acid oil mixture comprises at least 80% EPA and DHA by weight of the fatty acid oil mixture, of which at least 95% is EPA. In yet another embodiment, the fatty acid oil mixture comprises at least 90% EPA and DHA by weight of the fatty acid oil mixture, of which at least 95% is EPA.

[0106] In another embodiment, the fatty acid oil mixture comprises at least 75% EPA and DHA by weight of the fatty acid oil mixture, of which at least 95% is DHA. For example, in one embodiment, the fatty acid oil mixture comprises at least 80% EPA and DHA by weight of the fatty acid oil mixture, of which at least 95% is DHA. In another embodiment, the fatty acid oil mixture comprises at least 90% EPA and DHA by weight of the fatty acid oil mixture, of which at least 95% is DHA.

Supplement

[0107] The present disclosure further provides a food supplement or a nutritional supplement comprising a fatty acid oil mixture and at least one fatty acid, wherein the fatty acid oil mixture comprises less than 75% EPA and DHA by weight of the fatty acid oil mixture. In some embodiments, for example, the fatty acid oil comprises less than 70% EPA and DHA by weight of the fatty acid oil mixture, such as less than 65%, less than 60%, less than 55%, less than 50%, less than 45%, less than 40%, or even less than 35% by weight of the fatty acid oil mixture.

[0108] In some embodiments, the fatty acid oil mixture comprises from about 25% to about 75% EPA and DHA by weight of the fatty acid oil mixture, such as from about 30% to about 75%, from about 30% to about 70%, from about 30% to about 65%, from about 30% to about 55%, from about 30% to about 50%, from about 30% to about 45%, from about 30% to about 40%, and further for example, from about 30% to about 35% EPA and DHA, by weight of the fatty acid oil mixture.

[0109] In some embodiments of the present disclosure, the fatty acids, such as omega-3 fatty acids, of the fatty acid oil mixture are esterified, such as alkyl esters. The alkyl esters may include, but are not limited to, ethyl, methyl, propyl, and butyl esters, and mixtures thereof. In other embodiments, the fatty acids are chosen from mono-, di-, and triglycerides. For example, the fatty acid oil mixture comprises from about 25% to about 75% EPA and DHA, by weight of the fatty acid oil mixture in a form chosen from methyl ester, ethyl ester, and triglyceride.

Compositions

[0110] In some embodiments, the fatty acid oil mixture comprises from about 50% to about 95% by weight and the at least one free fatty acid comprises from about 5% to about 50% by weight, each relative to the total weight of the composition.

[0111] The compositions presently disclosed may be in a tablet form or in a capsule form.

Superdisintegrant

[0112] The compositions presently disclosed may further comprise at least one superdistintegrant. Superdisintegrants may, for example, improve disintegrant efficiency resulting in decreased use levels in comparison to traditional disintegrants. Examples of superdisintegrants include, but are not limited to, crosscarmelose (a crosslinked cellulose), crospovidone (a crosslinked polymer), sodium starch glycolate (a crosslinked starch), and soy polysaccharides. Commercial examples of superdisintegrants include Kollidon® (BASF), Polyplasdone® XL (ISP), and Ac-Di-Sol (FMC BioPolymer).

[0113] In some embodiments of the present disclosure, the composition comprises from about 1% to about 25% of at least one superdisintegrant by weight of the composition, such as from about 1% to about 20% by weight, or from about 1% to about

15% by weight of the composition. In some embodiments, the compositions comprising at least one superdisintegrant are in a tablet form.

Surfactant / Preconcentrate

[0114] The present disclosure further provides for a preconcentrate composition. In some embodiments of the present disclosure, the composition further comprises at least one surfactant to form a preconcentrate. As used herein, the term "preconcentrate" refers to a composition comprising a fatty acid oil mixture, at least one free fatty acid, and at least one surfactant.

[0115] A surfactant may, for example, lower the surface tension of a liquid or the surface tension between two liquids. For example, surfactants according to the present disclosure may lower the surface tension between the fatty acid oil mixture and/or the at least one free fatty acid and an aqueous solution.

[0116] Chemically speaking, surfactants are molecules with at least one hydrophilic part and at least one hydrophobic (i.e., lipophilic) part. Surfactant properties may be reflected in the hydrophilic-lipophilic balance (HLB) value of the surfactant, wherein the HLB value is a measure of the degree of hydrophilic versus lipophilic properties of a surfactant. The HLB value normally ranges from 0 to 20, where a HLB value of 0 represents high hydrophilic character, and a HLB of 20 represents high lipophilic character. Surfactants are often used in combination with other surfactants, wherein the HLB values are additive. The HLB value of surfactant mixtures may be calculated as follows:

$$HLB_A \text{ (fraction of surfactant A)} + HLB_B \text{ (fraction of surfactant B)} = HLB_{A+B \text{ mixture}}$$

[0117] Surfactants are generally classified as ionic surfactants, e.g., anionic or cationic surfactants, and nonionic surfactants. If the surfactant contains two oppositely charged groups, the surfactant is named a zwitterionic surfactant. Other types of surfactants include, for example, phospholipids.

[0118] In at least one embodiment of the present disclosure, the composition comprises at least one surfactant chosen from nonionic, anionic, cationic, and zwitterionic surfactants.

[0119] Non-limiting examples of nonionic surfactants suitable for the present disclosure are mentioned below.

[0120] Pluronic® surfactants are nonionic copolymers composed of a central hydrophobic polymer (polyoxypropylene(poly(propylene oxide))) with a hydrophilic polymer (polyoxyethylene(poly(ethylene oxide))) on each side. Various commercially-available Pluronic® products are listed in Table 1.

Table 1: Examples of Pluronic® surfactants.

	Type	Average Molecular Weight (D)	HLB Value
Pluronic® L-31	Non-ionic	1100	1.0-7.0
Pluronic® L-35	Non-ionic	1900	18.0-23.0
Pluronic® L-61	Non-ionic	2000	1.0-7.0
Pluronic® L-81	Non-ionic	2800	1.0-7.0
Pluronic® L-64	Non-ionic	2900	12.0-18.0
Pluronic® L-121	Non-ionic	4400	1.0-7.0
Pluronic® P-123	Non-ionic	5800	7-9
Pluronic® F-68	Non-ionic	8400	> 24
Pluronic® F-108	Non-ionic	14600	> 24

[0121] Brij® are nonionic surfactants comprising polyethylene ethers. Various commercially-available Brij® products are listed in Table 2.

Table 2: Examples of Brij® surfactants.

	Type	Compound	HLB Value
Brij® 30	Non-ionic	Polyoxyethylene(4) lauryl ether	9.7
Brij® 35	Non-ionic	polyoxyethylene (23) lauryl ether	16.9
Brij® 52	Non-ionic	Polyoxyethylene (2) cetyl ether	5.3
Brij® 56	Non-ionic	Polyoxyethylene (10) cetyl ether	12.9
Brij® 58	Non-ionic	Polyoxyethylene (20) cetyl ether	15.7
Brij® 72	Non-ionic	polyoxyethylene (2) stearyl ether	4.9
Brij® 76	Non-ionic	polyoxyethylene (10) stearyl ether	12.4
Brij® 78	Non-ionic	polyoxyethylene (20) stearyl ether	15.3
Brij® 92V	Non-ionic	Polyoxyethylene (2) oleyl ether	4.9
Brij® 93	Non-ionic	Polyoxyethylene (2) oleyl ether	4
Brij® 96V	Non-ionic	polyethylene glycol oleyl ether	12.4
Brij® 97	Non-ionic	Polyoxyethylene (10) oleyl ether	12
Brij® 98	Non-ionic	Polyoxyethylene (20) oleyl ether	15.3
Brij® 700	Non-ionic	polyoxyethylene (100) stearyl ether	18

[0122] Span® are nonionic surfactants comprising sorbitan esters. Span® is available from different sources including Aldrich. Various commercially-available Span® products are listed in Table 3.

Table 3: Examples of Span® surfactants.

	Type	Compound	HLB Value
Span® 20	Non-ionic	sorbitan monolaurate	8.6
Span® 40	Non-ionic	sorbitan monopalmitate	6.7
Span® 60	Non-ionic	sorbitan monostearate	4.7
Span® 65	Non-ionic	sorbitan tristearate	2.1
Span® 80	Non-ionic	sorbitan monooleate	4.3
Span® 85	Non-ionic	Sorbitan trioleate	1.8

[0123] Tween® (polysorbates) are nonionic surfactants comprising polyoxyethylene sorbitan esters. Various commercially-available Tween® products are listed in Table 4.

Table 4: Examples of Tween® surfactants.

	Type	Compound	HLB Value
Tween® 20	Non-ionic	polyoxyethylene (20) sorbitan monolaurate	16.0
Tween® 40	Non-ionic	polyoxyethylene (20) sorbitan monopalmitate	15.6
Tween® 60	Non-ionic	polyoxyethylene sorbitan monostearate	14.9
Tween® 65	Non-ionic	polyoxyethylene sorbitan tristearate	10.5
Tween® 80	Non-ionic	polyoxyethylene(20)sorbitan monooleate	15.0
Tween® 85	Non-ionic	polyoxyethylene sorbane trioleate	11.0

[0124] Myrj® are nonionic surfactants comprising polyoxyethylene fatty acid esters. Various commercially-available Myrj® products are listed in Table 5.

Table 5: Examples of Myrj® surfactants.

	Type	Compound	HLB Value
Myrj® 45	Non-ionic	polyoxyethylene monostearate	11.1
Myrj® 49	Non-ionic	polyoxyethylene monostearate	15.0
Myrj® 52	Non-ionic	polyoxyethylene monostearate	16.9
Myrj® 53	Non-ionic	polyoxyethylene monostearate	17.9

[0125] Cremophor® are nonionic surfactants. Various commercially-available Cremophor® products are listed in Table 6.

Table 6: Examples of Cremophor® surfactants.

	Type	Compound	HLB Value
Cremophor® REL	Non-ionic	polyoxyethylated castor oil	2-14
Cremophor® RH40	Non-ionic	hydrogenated polyoxyethylated castor oil	14-16
Cremophor® RH60	Non-ionic	hydrogenated polyoxyethylated castor oil	15-17
Cremophor® RO	Non-ionic	hydrogenated polyoxyethylated castor oil	16.1

[0126] According to the present disclosure, other exemplary nonionic surfactants include, but are not limited to, diacetyl monoglycerides, diethylene glycol monopalmitostearate, ethylene glycol monopalmitostearate, glyceryl behenate, glyceryl distearate, glyceryl monolinoleate, glyceryl mono-oleate, glyceryl monostearate, macrogol cetostearyl ether such as cetomacrogol 1000 and polyoxy 20 cetostearyl ether, macrogol 15 hydroxystearate, macrogol lauril ethers such as laureth 4 and lauromacrogol 400, macrogol monomethyl ethers, macrogol oleyl ethers such as polyoxyl 10 oleyl ether, macrogol stearates such as polyoxyl 40 stearate, menfegol, mono and diglycerides, nonoxinols such as nonoxinol-9, nonoxinol-10 and nonoxinol-11, octoxinols such as octoxinol 9 and oxtoxinol 10, polyoxamers such as polyoxalene, polyoxamer 188, polyoxamer 407, polyoxyl castor oil such as polyoxyl 35 castor oil, polyoxyl hydrogenated castor oil such as polyoxyl 40 hydrogenated castor oil, propylene glycol diacetate, propylene glycol laurates such as propylene glycol dilaurate and propylene glycol monolaurate. Further examples include propylene glycol monopalmitostearate, quillaia, sorbitan esters, and sucrose esters.

[0127] Anionic surfactants suitable for the present disclosure include, for example, salts of perfluorocarboxylic acids and perfluorosulphonic acid, alkyl sulphate salts such as sodium dodecyl sulphate and ammonium lauryl sulphate, sulphate ethers such as sodium lauryl ether sulphate, and alkyl benzene sulphonate salts.

[0128] Cationic surfactants suitable for the present disclosure include, for example, quaternary ammonium compounds such as benzalkonium chloride, cetylpyridinium chlorides, benzethonium chlorides, and cetyl trimethylammonium bromides or other trimethylalkylammonium salts.

[0129] Zwitterionic surfactants include, but are limited to, for example dodecyl betaines, coco amphoglycinates and cocamidopropyl betaines.

[0130] In some embodiments of the present disclosure, the surfactant may comprise a phospholipid, derivative thereof, or analogue thereof. Such surfactants may, for example, be chosen from natural, synthetic, and semisynthetic phospholipids, derivatives thereof, and analogues thereof. Exemplary phospholipids surfactants include

phosphatidylcholines with saturated, unsaturated and/or polyunsaturated lipids such as dioleoylphosphatidylcholine, dipentadecanoylphosphatidylcholine, dilauroylphosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine, distearoylphosphatidylcholine, di-eicopentaenoyl(EPA)choline, didocosahexaenoyl(DHA)choline, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines and phosphatidylinositols. Other exemplary phospholipid surfactants include soybean lecithin, egg lecithin, diolelyl phosphatidylcholine, distearoyl phosphatidyl glycerol, PEG-ylated phospholipids, and dimyristoyl phosphatidylcholine.

[0131] Phospholipids may be "natural" or from a marine origin chosen from, e.g. phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine and phosphatidylinosytol. The fatty acid moiety may be chosen from 14:0, 16:0, 16: 1n-7, 18:0, 18:1n-9, 18:1n-7, 18:2n-6, 18:3n-3, 18:4n-3, 20:4n-6, 20:5n-3, 22:5n-3 and 22:6n-3, or any combinations thereof. In one embodiment, the fatty acid moiety is chosen from palmitic acid, EPA and DHA.

[0132] Other exemplary surfactants suitable for the present disclosure are listed in Table 7.

Table 7: Other surfactants

Surfactant	Type	HBL Value
Ethylene glycol distearate	Nonionic	1.5
Glyceryl monostearate	Nonionic	3.3
Propylene glycol monostearate	Nonionic	3.4
Glyceryl monostearate	Nonionic	3.8
Diethylene glycol monolaurate	Nonionic	6.1
Acacia	Anionic	8.0
Cetrimonium bromide	Cationic	23.3
Cetylpyridinium chloride	Cationic	26.0
Polyoxamer 188	Nonionic	29.0
Sodium lauryl sulphate	Anionic	40

[0133] In some embodiments of the present disclosure, the at least one surfactant does not comprise Labrasol, Cremophor RH40, or the combination of Cremophor and Tween-80.

[0134] In some embodiments, the at least one surfactant has a hydrophilic-lipophilic balance (HLB) of less than about 10, such as less than about 9, or less than about 8.

Co-surfactant

[0135] In some embodiments, compositions of the present disclosure further comprise at least one co-surfactant. As used herein the term "co-surfactant" means a substance added to, e.g., the preconcentrate in combination with the at least one surfactant to affect, e.g., increase or enhance, emulsification and/or stability of the preconcentrate, for example to aid in forming an emulsion. In some embodiments, the at least one co-surfactant is hydrophilic.

[0136] Examples of co-surfactants suitable for the present disclosure include, but are not limited to, short chain alcohols comprising from 1 to 6 carbons (e.g., ethanol), benzyl alcohol, alkane diols and triols (e.g., propylene glycol, glycerol, polyethylene glycols such as PEG and PEG 400), glycol ethers such as tetraglycol and glycofurol (e.g., tetrahydrofurfuryl PEG ether), pyrrolidine derivatives such as N-methyl pyrrolidone (e.g., Pharmasolve®) and 2-pyrrolidone (e.g., Soluphor® P), and bile salts, for example sodium deoxycholate. Further examples include ethyl oleate.

[0137] In some embodiments, the at least one co-surfactant comprises from about 1% to about 10%, by weight relative to the weight of the preconcentrate.

Solvent

[0138] In some embodiments, compositions of the present disclosure, such as the preconcentrate, further comprises at least one solvent. Hydrophilic solvents suitable for the present disclosure include, but are not limited to, alcohols, including water-miscible alcohols, such as absolute ethanol and/or glycerol, and glycols, for example glycols obtainable from an oxide such as ethylene oxide, such as 1,2-propylene glycol. Other non-limiting examples include polyols, such as polyalkylene glycol, e.g., poly(C_{2-3})alkylene glycol such as polyethylene glycol.

[0139] In some embodiments of the present disclosure, the preconcentrate comprises at least one substance that acts both as a co-surfactant and a solvent, for example an alcohol such as ethanol. In other embodiments, the preconcentrate comprises at least one co-surfactant and at least one solvent that are different substances. For example, in some embodiments the preconcentrate comprises ethanol as the co-surfactant and glycerol as the solvent.

[0140] In some embodiments of the present disclosure, the preconcentrate is a pharmaceutical preconcentrate comprising a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant.

[0141] In one embodiment, the pharmaceutical preconcentrate comprises: a fatty acid oil mixture comprising at least 95% of EPA ethyl ester, DHA ethyl ester, or mixtures

thereof, by weight of the fatty acid oil mixture; at least one free fatty acid chosen from linoleic, α-linolenic acid (ALA), γ-linoleic acid (GLA), and oleic acid; and a least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof.

[0142] In another embodiment, the pharmaceutical preconcentrate comprises: a fatty acid oil mixture comprising from about 80% to about 88% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; at least one free fatty acid comprising oleic acid; and at least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof; wherein the at least one surfactant comprises less than 40%, by weight relative to the weight of the preconcentrate.

[0143] In another embodiment, the pharmaceutical preconcentrate comprises: a fatty acid oil mixture comprising from about 80% to about 88% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; at least one free fatty acid comprising linoleic acid; and at least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof; wherein the at least one surfactant comprises less than 35%, by weight relative the weight of the preconcentrate.

[0144] In another embodiment, the pharmaceutical preconcentrate comprises: a fatty acid oil mixture comprising from about 80% to about 88% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form; at least one free fatty acid comprising from about 80% to about 88% EPA and DHA, by weight of the at least one free fatty acid, wherein the EPA and DHA are in free acid form; and at least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof. For example, the pharmaceutical preconcentrate may comprise K85EE as the fatty acid oil mixture, K85FA as the at least one free fatty acid, and at least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof.

[0145] In another embodiment, the pharmaceutical preconcentrate may comprise K85EE as the fatty acid oil mixture, K85FA as the at least one free fatty acid, and at least one surfactant chosen from polysorbate 20 or polysorbate 80, wherein the [K85EE]:[Tween]:[K85FA] ranges from e.g. about 5:2:0.5 to 5:4:2. In a further embodiment, the ration between [K85EE]:[Tween]:[K85FA] is about [4-5]:[3-4]:[1-1.5].

[0146] In another embodiment, minimum of about 5-10% up to maximum of about 50% of fatty acid oil mixture comprising from about 80% to about 88% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form, is substituted by a free fatty acid chosen from a K85-FA composition (corresponding to a K85-FA fatty acid profile achieved by hydrolyzing a K85-EE fatty acid ethyl ester composition) EPA, DPA, DHA, and combinations thereof. For example, the EPA-EE and DHA-EE content from 400 mg/g to 840 mg/g of total fatty acid oil mixture is replaced by 40 to 440 mg/g Free fatty acid chosen from a K85-FA composition.

[0147] In other embodiments, the preconcentrate is a food supplement or nutritional supplement preconcentrate comprising a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant.

[0148] In some embodiments, the weight ratio of fatty acid oil mixture:surfactant of the preconcentrate ranges from about 1:1 to about 10:1, from about 1.1 to about 8:1, from 1:1 to about 7:1, from 1:1 to about 6:1, from 1:1 to about 5:1, from 1:1 to about 4:1, from 1:1 to about 3:1, or from 1:1 to about 2:1.

[0149] In some embodiments, the at least one surfactant comprises from about 5% to about 55%, by weight relative to the total weight of the preconcentrate. For example, in some embodiments, the at least one surfactant comprises from about 5% to about 35%, from about 10% to about 35%, from about 15% to about 35%, from about 15% to about 30%, or from about 20% to about 30%, by weight, relative to the total weight of the preconcentrate.

SNEDDS/SMEDDS/SEDDS

[0150] The preconcentrate of the present disclosure may be in a form of a self-nanoemulsifying drug delivery system (SNEDDS), a self-microemulsifying drug delivery system (SMEDDS), or a self emulsifying drug delivery system (SEDDS), wherein the preconcentrate forms an emulsion in an aqueous solution.

[0151] Without being bound by theory, it is believed that the preconcentrate forms a SNEDDS, SMEDDS, and/or SEDDS upon contact with gastric and/or intestinal media in the body, wherein the preconcentrate forms an emulsion comprising micelle particles. The emulsion may, for example, provide for increased or improved stability of the fatty acids for uptake in the body and/or provide increased or improved surface area for absorption. SNEDDS/SMEDDS/SEDDS may thus provide for enhanced or improved hydrolysis, solubility, bioavailability, absorption, or any combinations thereof of fatty acids in vivo.

[0152] Generally, known SNEDDS/SMEDDS/SEDDS formulations comprise ~10 mg of a drug and ~500 mg of surfactants/co-surfactants. The SNEDDS/SMEDDS/SEDDS presently disclosed may have the opposite relationship, i.e., the amount of fatty acid oil mixture comprising the active pharmaceutical ingredient (API) is greater than the amount of surfactant.

[0153] The SNEDDS/SMEDDS/SEDDS presently disclosed may comprise a particle size (i.e., particle diameter) ranging from about 5 nm to about 10 μm. For example, in some embodiments, the particle size ranges from about 5 nm to about 1 μm,

such as from about 50 nm to about 750 nm, from about 100 nm to about 500 nm, or from about 150 nm to about 350 nm.

Excipients

[0154] The compositions, preconcentrates, and/or SNEDDS/SMEDDS/SEDDS presently disclosed may further comprise at least one non-active pharmaceutical ingredient, e.g., excipient. Non-active ingredients may solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, protect, color, flavor, and/or fashion active ingredients into an applicable and efficacious preparation, such that it may be safe, convenient, and/or otherwise acceptable for use. The at least one non-active ingredient may be chosen from colloidal silicon dioxide, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium stearyl fumarate, talc, titanium dioxide, and xanthum gum.

[0155] The compositions, preconcentrates, and/or SNEDDS/SMEDDS/SEDDS presently disclosed may further comprise at least one antioxidant. Examples of antioxidants suitable for the present disclosure include, but are not limited to, α-tocopherol (vitamin E), calcium disodium EDTA, alpha tocoferyl acetates, butylhydroxytoluenes (BHT), and butylhydroxyanisoles (BHA).

[0156] The compositions presently disclosed may be administered, e.g., in capsule, tablet or any other drug delivery forms. For example, the compositions and/or preconcentrates presently disclosed may be encapsulated, such as a gelatin capsule.

[0157] In some embodiments of the present disclosure, the capsule fill content ranges from about 0.400 g to about 1.600 g. For example, in some embodiments, the capsule fill content ranges from about 0.400 g to about 1.300 g, from about 0.600 g to about 1.200 g, from about 0.600 g to about 0.800 g, from about 0.800 g to about 1.000, from about 1.000 g to about 1.200 g, or any amount in between. For example, in some embodiments the capsule fill content is about 0.600 g, about 0.800 g, about 1.000 g, or about 1.200 g.

[0158] The capsules presently disclosed may be manufactured in low oxygen conditions to inhibit oxidation during the manufacturing process. Preparation of capsules and/or microcapsules in accordance with the present disclosure may be carried out following any of the methods described in the literature. Examples of such methods include, but are not limited to, simple coacervation methods (see, e.g., ES 2009346, EP 0052510, and EP 0346879), complex coacervation methods (see, e.g., GB 1393805), double emulsion methods (see, e.g., U.S. 4,652,441), simple emulsion methods (see, e.g., U.S. 5,445,832), and solvent evaporation methods (see, e.g., GB 2209937). Those methods may, for example, provide for continuous processing and flexibility of batch size.

Methods or Uses

[0159] The present disclosure further encompasses methods of treating and/or regulating at least one health problem in a subject in need thereof. The compositions presently disclosed may be administered, e.g., in capsule, tablet or any other drug delivery forms, to a subject for therapeutic treatment and/or regulation of at least one health problem including, for example, irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction. In some embodiments, the at least one health problem is chosen from mixed dyslipidemia, dyslipidemia, hypertriglyceridemia, hypercholesterolemia, heart failure, and post-myocardial infarction.

[0160] In one embodiment, the present disclosure provides for a method of treating at least one health problem in a subject in need thereof, comprising administering to the subject a pharmaceutical composition comprising a pharmaceutically-effective amount of a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid. In some embodiments, the method treats at least one of elevated triglyceride levels, non-HDL cholesterol levels, LDL cholesterol levels and/or VLDL cholesterol levels. For example, the method may reduce triglyceride levels from about 30% to about 80%, such as from about 40% to about 70%, from about 40% to about 60%, or from about 30% to about 50%, in a subject with elevated triglyceride levels.

[0161] In another embodiment, the present disclosure provides for a method of regulating at least one health problem in a subject in need thereof, comprising administering to the subject administering to the subject a supplement composition comprising: a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid; wherein the at least one health problem is chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

[0162] In still a further embodiment, the present disclosure provides for a method for enhancing at least one parameter chosen from hydrolysis, solubility, bioavailability, absorption, and combinations thereof of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) comprising combining: a fatty acid oil mixture comprising EPA and DHA in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid. For example, combining: a fatty acid oil mixture comprising EPA and DHA in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one

surfactant; wherein the fatty acid oil mixture, that at least one free fatty acid, and the at least one surfactant form a preconcentrate. In addition, the preconcentrate can form a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) in an aqueous solution. The bioavailablity may be increased by at least 40%, such as by about 80% or by at least 85%.

[0163] In some embodiments, the pharmaceutical composition or supplement composition further comprises at least one surfactant to form a preconcentrate for administration to a subject in need thereof to treat and/or regulate at least one health problem. In some embodiments, the preconcentrate forms a self-nanoemulsifying drug delivery system (SNEDDS), a self-microemulsifying drug delivery system (SMEDDS), or a self-emulsifying drug delivery system (SEDDS) in an aqueous solution. In some embodiments, the aqueous solution is gastric media and/or intestinal media.

[0164] The total daily dosage of the fatty acid oil mixture may range from about 0.600 g to about 6.000 g. For example, in some embodiments, the total dosage of the fatty acid oil mixture ranges from about 0.800 g to about 4.000 g, from about 1.000 g to about 4.000 g, or from about 1.000 g to about 2.000 g. In one embodiment, the fatty acid oil mixture is chosen from K85EE and AGP 103 fatty acid oil compositions.

[0165] The composition and/or preconcentrates presently disclosed may be administered in from 1 to 10 dosages, such as from 1 to 4 times a day, such as once, twice, three times, or four times per day, and further for example, once, twice or three times per day. The administration may be oral or any other form of administration that provides a dosage of fatty acids, e.g., omega-3 fatty acids, to a subject.

[0166] The following examples are intended to illustrate the present disclosure without, however, being limiting in nature. It is understood that the skilled artisan will envision additional embodiments consistent with the disclosure provided herein.

EXAMPLES

[0167] **Example 1: Preconcentrates**

[0168] Different preconcentrates were prepared as described in Table 9. To prepare the preconcentrates, the components were mixed according to the schemes identified below on a weight to weight basis. The preconcentrates were visually inspected after mixing and again after being stored for 24 hours at room temperature. Under the Preconcentrate heading, a "clear" designation represents a transparent homogenous mixture; an "unclear" designation represents a nonhomogenous mixture,

where some turbidity can be observed by visual inspection. The degree of turbidity was not determined.

[0169] All clear preconcentrates were emulsified in gastric media, by adding gastric media (2 ml) to approximately 100 mg of the preconcentrate. The composition of the gastric media is shown in Table 8.

Table 8: Composition of Gastric Media.

Gastric Media	
Bile salts, Porcine (mM)	0.08
Lechitin(mM)	0.02
Sodium chloride (mM)	34.2
Pepsin (mg/ml)	0.1
pH	1.6 (adjust with 1 M HCl)
Osmolarity(mOsm/kg)	120

[0170] The outcome of the emulsification was recorded approximately 3 hours after mixing. A majority of the preconcentrates formed milky emulsions immediately after mixing. Emulsions that stayed milky and homogenous after 3 hours are described as "milky," under the Emulsion heading. Emulsions that separated or became nonhomogenous or where oil drops were observed are described as "separates," under the Emulsion heading.

[0171] Selected emulsions were further characterized by determining the particle size. Particle size was measured using a Malvern Zetasizer (Malvern Instrument, Worcestershire, UK) with particle size measuring range of 0.5 - 6000 nm and Zeta potential of particle range of 3 nm - 10 µm. The particle size was measured in triplicate. The K85EE (EE = ethyl ester) fatty acid composition used herein is sold in a gelatin capsule and branded primarily under the trademarks Lovaza™ or Omacor®.

Table 9: Preconcentrates.

No.	K85-EE (mg)	Tween-20 (mg)	Oleic Acid (mg)	Total vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
1	451.4	234.3	99	784.7	57:29:12	Unclear	-	-
2	448.8	299.7	53.8	802.3	55:37:6	Unclear	-	-

3	451.2	324.7	24.7	800.6	56:40:3	Unclear	-	-
10	400	300	100	800	50:37:12	Clear	Milky	271
11	404	298	97	799	50:37:12	Clear	Milky	-
12	500	300	217	1017	49:29:21	Clear	Separates	-
13	398	300	99	797	49:37:12	Clear	Milky	257
14	399	252	98	749	53:33:13	Clear	Separates	226
15	400	204	102	706	56:28:14	Clear	Separates	199
21	450	198	133	781	57:25:17	Clear	Separates	-
23	549	204	169	922	59:22:18	Clear	Separates	-
24	600	200	178	978	61:20:18	Clear	Separates	-
26	453	214	121	788	57:27:15	Clear	Separates	-
27	456	220	121	797	57:27:15	Clear	Separates	-
28	452	228	144	824	54:27:17	Clear	Separates	-
29	448	230	122	800	56:28:15	Clear	Separates	-
30	452	242	124	818	55:29:15	Clear	Separates	-
31	449	251	124	824	54:30:15	Clear	Milky	-
32	448	260	123	831	53:31:14	Clear	Separates	-
33	452	270	121	843	53:32:14	Clear	Separates	-
34	449	281	123	853	52:32:14	Clear	Separates	-
35	448	290	121	859	52:33:14	Clear	Separates	-

No.	K85-EE (mg)	Tween-20 (mg)	Ricinoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
36	402	298	98	798	50:37:12	Clear	Milky	277
37	402	250	100	752	53:33:13	Clear	Milky	268
38	400	200	100	700	57:28:14	Unclear	-	-
39	450	250	100	800	56:31:12	Clear	Milky	-
43	400	110	100	610	65:18:16	Clear	Separates	-
44	500	270	105	875	57:30:12	Clear	Separates	-
45	505	295	103	903	55:32:11	Clear	Milky	-

46	525	250	143	918	57:27:15	Clear	Separates	-
47	500	252	118	870	57:28:13	Clear	Separates	-
48	297	293	145	735	40:39:19	Clear	Separates	-
49	500	260	127	887	56:29:14	Clear	Separates	-
50	499	285	106	890	56:32:11	Clear	Separates	-
51	403	298	193	894	45:33:21	Clear	Milky	-
52	460	250	90	800	57:31:11	Clear	-	-

No.	K85-EE (mg)	Tween-40 (mg)	Ricinoleic acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
53	450	255	98	803	56:31:12	Clear	Milky	237
55	498	220	98	816	61:26:12	Clear	Milky	226
56	505	202	106	813	62:24:13	Clear	Separates	-
57	500	200	100	800	62:25:12	Clear	Separates	-
58	552	152	102	806	68:18:12	Clear	Separates	-

No.	K85-EE (mg)	Tween-60 (mg)	Ricinoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
70	500	200	100	800	62:25:12	Clear	Milky	-
71	500	150	100	750	66:20:13	Clear	Separates	-
72	529	180	104	813	65:22:12	Clear	Separates	-
73	518	200	102	820	63:24:12	Clear	Separates	-

No.	K85-EE (mg)	Tween-80 (mg)	Ricinoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
54	450	270	105	825	54:32:12	Clear	Separates	-

No.	K85-EE (mg)	Cremophor EL (mg)	Ricinoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
40	399.9	300	106.4	806.3	49:37:13	Unclear	-	-
41	400	256.9	137	793.9	50:32:17	Unclear	-	-

No.	K85-EE (mg)	Soritol (mg)	Ricinoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
42	400	211	104	715	55:29:14	Clear/solid when cooled	-	-

No.	K85-EE (mg)	PEG-400 (mg)	Ricinoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
16	399.9	310.2	162.6	872.7	45:35:18	Clear	Separates	-
17	398.3	256.8	157.9	813	48:31:19	Clear	Separates	-
18	402.4	198.7	147.5	748.6	53:26:19	Clear	Separates	-

No.	K85-EE (mg)	Tween-20 (mg)	PEG-400 (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
19	398.2	297.9	214.7	910.8	43:32:23	Unclear	-	-
20	403	248.2	145.3	796.5	50:31:18	Unclear	-	-

No.	K85-EE (mg)	Tween-20 (mg)	α-Linoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
74	402	300	100	802	50:37:12	Clear	Milky	-
75	454	249	98	801	56:31:12	Slightly dense	Separates	-
76	502	204	103	809	62:25:12	Slightly dense	Separates	-

No.	K85-EE (mg)	Tween-40 (mg)	α-Linoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
77	403	299	108	810	49:36:13	Clear / Precip-itate	Separates	-
78	456	252	110	818	55:30:13	Clear / Precip-itate	Separates	-
79	503	217	103	823	61:26:12	Clear / Precip-itate	Separates	-

No.	K85-EE (mg)	Tween-60 (mg)	α-Linoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)

80	402	313	104	819	49:38:12	Clear	Separates	-
81	459	205	100	764	60:26:13	Clear	Separates	-
82	498	198	106	802	62:24:13	Clear	Separates	-

No.	K85-EE (mg)	Tween-80 (mg)	α-Linoleic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
83	407	317	102	826	49:38:12	Clear	Milky	261.3
84	455	256	110	821	55:31:13	Clear	Milky	260.8
85	498	208	102	808	61:25:12	Clear	Milky	274.5

No.	K85-EE (mg)	Tween-20 (mg)	Erucuc Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
86	401	300	99	800	50:37:12	Clear	Semi Milky	-
87	451	250	105	806	55:31:13	Clear	Separates	-
88	504	204	102	810	62:25:12	Clear	Separates	-

No.	K85-EE (mg)	Tween-40 (mg)	Erucuc Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
89	401	298	102	801	50:37:12	Clear	Separates	-
90	451	254	99	804	56:31:12	Clear	Separates	-
91	504	219	103	826	61:26:12	Clear	Separates	-

No.	K85-EE (mg)	Tween-60 (mg)	Erucuc Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
92	401	301	104	806	49:37:12	Clear	Separates	-
93	454	267	101	822	55:32:12	Clear	Separates	-
94	497	202	100	799	62:25:12	Clear	Separates	-

No.	K85-EE (mg)	Tween-60 (mg)	Erucuc Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
95	406	298	100	804	50:37:12	Clear	Separates	-
96	450	251	102	803	56:31:12	Clear	Separates	-

97	502	205	122	829	60:24:14	Clear	Separates	-

No.	K85-EE (mg)	Tween-20 (mg)	α-Linolenic acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
98	401	308	105	814	49:37:12	Clear	Milky, beginning separation	-
102	450	264	108	822	54:32:13	Clear	Milky, beginning separation	-
106	501	200	111	812	61:24:13	Clear	Milky, with separation	-

No.	K85-EE (mg)	Tween-40 (mg)	α-Linolenic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
99	402	302	102	806	49:37:12	Clear	Milky, beginning separation	-
103	452	254	101	807	56:31:12	Clear	Milky, with separation	-
107	502	206	108	816	61:25:13	Clear	Milky, with separation	-

No.	K85-EE (mg)	Tween-60 (mg)	α-Linolenic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
100	403	303	103	809	49:37:12	Clear	Milky, beginning separation	-
104	450	249	102	801	56:31:12	Clear	Milky, with separation	-
108	506	200	100	806	62:24:12	Unclear	Milky, beginning separation	-

No.	K85-EE (mg)	Tween-80 (mg)	α-Linolenic Acid (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
101	403	308	106	817	49:37:12	Clear	Milky, beginning separation	-
105	452	253	102	807	56:31:12	Clear	Milky, with separation	-
109	507	203	112	822	61:24:13	Clear	Milky, with separation	-

No.	K85-EE (mg)	Tween-20 (mg)	KE85-FA (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
110	398.5	300.5	98.6	797.6	49:37:12	Clear	Milky (<10min waiting time)	
111	448	245.9	110.4	804.3	55:30:13	Unclear	-	-
112	498.3	197.9	106.2	802.4	62:24:13	Unclear	-	-

No.	K85-EE (mg)	Tween-40 (mg)	KE85-FA (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
113	405.7	303.7	105.8	815.2	49:37:12	Clear	Milky (<10min waiting time)	-
114	452.8	261.6	101.8	816.2	55:32:12	Clear	Milky (<10min waiting time)	-
115	499	212.2	114.7	825.9	60:25:13	Clear	Milky (<10min waiting time)	-

No.	K85-EE (mg)	Tween-60 (mg)	KE85-FA (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
116	395	296.2	100	791.2	49:37:12	Clear	Milky (<10min waiting time)	-
117	450.3	253.1	98.2	801.6	56:31:12	Clear	Milky (<10min waiting time)	-
118	500.8	206	105.7	812.5	61:25:13	Clear	Milky (<10min waiting time)	-

No.	K85-EE (mg)	Tween-80 (mg)	KE85-FA (mg)	Total Vol. (mg)	Ratio	Pre-conc.	Emulsion	Particle Size (nm)
119	402	308.3	100.8	811.1	49:38:12	Clear	Milky, sticky (<10min waiting time)	-

120	456.6	260.3	103.5	820.4	55:31:12	Clear	Milky, sticky (<10min waiting time)	-
121	502.3	202.2	104	808.5	62:25:12	Clear	Milky, sticky (<10min waiting time)	-

[0172] Of the preconcentrates prepared, formulation number 85 facilitated a load of 60% K85EE into the preconcentrate and gave a stable emulsion in gastric media with a particle size determined to be about 275 nm. Attempts to prepare preconcentrates with saturated fatty acids, stearic acid and decanoic acid failed. Although homogenous preconcentrates could be obtained by heating, a precipitation of stearic acid or decanoic acid was observed upon cooling of the preconcentrate to room temperature.

[0173] **Example 2: Additional Preconcentrates**

[0174] Additional preconcentrates were prepared to determine an optimized amount of surfactant with K85EE and K85FA. The preconcentrates described in Table 10 were prepared as provided in Example 1. The preconcentrates were visually inspected after mixing and again after being stored for 24 hours at room temperature. Under the Preconcentrate heading, a "clear" designation represents a transparent homogenous mixture; a "turbid" designation represents a nonhomogenous mixture, where some turbidity can be observed by visual inspection. The degree of turbidity was not determined.

Table 10: Additional Preconcentrates.

K85-EE (mg)	Tween20 (mg)	K85FA (mg)	Preconcentrate
107	307	62	Turbid
107	307	76	Turbid
107	307	102	Turbid
107	307	200	Clear
107	307	401	Clear
107	307	803	Clear
107	307	1608	Clear
26	300	99	Clear
104	300	99	Clear
201	300	99	Clear
316	300	99	Clear
400	300	99	Clear

497	300	99	Turbid
618	300	99	Turbid
405	42	101	Clear
405	99	101	Clear
405	202	101	Clear
405	299	101	Clear
405	400	101	Clear
405	618	101	Clear
405	1000	101	Clear
K85-EE (mg)	**Tween80 (mg)**	**K85FA (mg)**	**Preconcentrate**
407	306	57	Clear
407	306	80	Clear
407	306	103	Clear
407	306	202	Clear
407	306	401	Clear
28	299	101	Clear
57	299	101	Clear
99	299	101	Clear
233	299	101	Clear
316	299	101	Clear
414	299	101	Clear
510	299	101	Clear
569	299	101	Clear
627	299	101	Clear
688	299	101	Clear
769	299	101	Clear
402	32	106	Clear
402	126	106	Clear
402	229	106	Clear
402	326	106	Clear
402	410	106	Clear
402	997	106	Clear
K85-EE (mg)	**Tween-40 (mg)**	**K85FA (mg)**	**Preconcentrate**
111	311	59	Turbid
111	311	70	Clear
111	311	95	Clear
111	311	135	Clear

111	311	244	Clear
111	311	798	Clear
111	311	1567	Clear
30	309	98	Clear
110	309	98	Clear
208	309	98	Clear
322	309	98	Clear
404	309	98	Clear
501	309	98	Turbid
618	309	98	Turbid
408	38	99	Clear
408	105	99	Clear
408	210	99	Clear
408	301	99	Clear
408	398	99	Clear
408	616	99	Clear
408	1001	99	Clear

[0175] **Example 3: Compatibility of Preconcentrates with Solvents**

[0176] The compatibility of solvents and a preconcentrate having a fixed amount of K85EE and Tween-80 were evaluated. The preconcentrates described in Table 11 were prepared as provided in Example 1, but with the addition of the solvent identified below. The preconcentrates were visually inspected after mixing and again after being stored for 24 hours at room temperature. Under the Preconcentrate heading, a "clear" designation represents a transparent homogenous mixture; a "turbid" designation represents a non-homogenous mixture, where some turbidity can be observed by visual inspection. The degree of turbidity was not determined.

Table 11: Compatibility of Solvent and Preconcentrates.

K85-EE (mg)	Tween-80 (mg)	96% ethanol (mg)	96% ethanol (%)	Preconcentrate
400	110	10.7	2.1	Turbid
400	110	18.7	3.5	Turbid
400	110	28.4	5.3	Turbid
400	110	32.1	5.9	Turbid
400	110	45.7	8.2	Turbid
400	110	53.5	9.5	Turbid
400	110	61.5	10.8	Turbid
400	110	69.8	12.0	Turbid

400	110	79.9	13.5	Turbid
400	110	91.3	15.2	Turbid
400	110	102.5	16.7	Turbid
K85-EE (mg)	**Tween-80 (mg)**	**Propylene glycol (mg)**	**Propylene glycol (%)**	**Preconcentrate**
400	110	11.1	2.1	Turbid
400	110	16.7	3.2	Turbid
400	110	23.1	4.3	Turbid
400	110	32.9	6.1	Turbid
400	110	41.5	7.5	Turbid
400	110	48.6	8.7	Turbid
400	110	59.9	10.5	Turbid
400	110	72.9	12,5	Turbid
400	110	81.5	13.8	Turbid
400	110	93.5	15.5	Turbid
400	110	104.6	17.0	Turbid
K85-EE (mg)	**Tween-80 (mg)**	**PEG 300 (mg)**	**PEG 300 (%)**	**Preconcentrate**
400	110	13.9	2.7	Turbid
400	110	23.7	4.4	Turbid
400	110	35.6	6.5	Turbid
400	110	47.1	8.5	Turbid
400	110	55.0	9.7	Turbid
400	110	68.7	11.9	Turbid
400	110	81.8	13.8	Turbid
400	110	90.3	15.0	Turbid
400	110	104.0	16.9	Turbid
K85-EE (mg)	**Tween-80 (mg)**	**Benzyl alcohol (mg)**	**Benzyl alcohol (%)**	**Preconcentrate**
400	110	0	0	Clear
400	110	11.4	2.2	Turbid
400	110	18.1	3.4	Turbid
400	110	30.9	5.7	Clear
400	110	45.5	8.2	Clear
400	110	55.6	9.8	Clear
400	110	66.7	11.6	Clear
400	110	77.4	13.2	Clear
400	110	92.1	15.3	Clear
400	110	99.0	16.3	Clear
K85-EE (mg)	**Tween-80 (mg)**	**Triacetin (mg)**	**Triacetin (%)**	**Preconcentrate**

400	110	12.3	2.4	Turbid
400	110	24.3	4.5	Turbid
400	110	35.8	6.6	Turbid
400	110	45.3	8.2	Turbid
400	110	57.0	10.1	Turbid
400	110	68.1	11.8	Turbid
400	110	80.9	13.7	Turbid
400	110	90.0	15.0	Turbid
400	110	101.7	16.6	Turbid
K85-EE (mg)	**Tween-80 (mg)**	**1-octadecanol 99% (mg)**	**1-octadecanol 99% (%)**	**Preconcentrate**
400	110	8.6	1.7	Precipitate
K85-EE (mg)	**Tween-80 (mg)**	**oleyl alcohol 85% (mg)**	**oleyl alcohol 85% (%)**	**Preconcentrate**
400	100	13.0	2.5	Turbid
400	100	26.5	4.9	Turbid
400	100	37.3	6.8	Turbid
400	100	49.5	8.8	Turbid
400	100	62.6	10.9	Turbid
400	100	77.7	13.2	Turbid
400	100	92.2	15.3	Turbid
400	100	105.7	17.2	Turbid
K85-EE (mg)	**Tween-80 (mg)**	**1-tetradecanol 97% (mg)**	**1 tetradecanol 97% (%)**	**Preconcentrate**
400	100	1.7	0.3	Turbid
400	100	10.3	2.0	Turbid
400	100	22.7	4.3	Turbid
400	100	35.8	6.6	Precipitate
K85-EE (mg)	**Tween-80 (mg)**	**glycerol (mg)**	**glycerol (%)**	**Preconcentrate**
400	100	17.7	3.4	Turbid
400	100	28.0	5.2	Turbid
400	100	41.7	7.6	Turbid
400	100	52.8	9.4	Turbid
400	100	71.2	12.3	Turbid
400	100	85.4	14.3	Turbid
400	100	92.3	15.3	Turbid
400	100	105.7	17.2	Turbid
K85-EE (mg)	**Tween-80 (mg)**	**Oleic acid 90 % (mg)**	**Oleic acid 90% (%)**	**Preconcentrate**

400	100	13.2	2.5	Turbid
400	100	23.9	4.5	Turbid
400	100	31.5	5.8	Turbid
400	100	41.4	7.5	Turbid
400	100	51.8	9.2	Turbid
400	100	65.2	11.3	Clear
400	100	79.8	13.5	Clear
400	100	87.2	14.6	Clear
400	100	102.2	16.7	Clear
K85-EE (mg)	**Tween-80 (mg)**	**1-docosanol 98% (mg)**	**1-docosanol 98% (%)**	**Preconcentrate**
400	100	9.6	1.8	Precipitate

[0177] **Example 4: Characterization of Preconcentrates and SNEDDS/SMEDDS/SEDDS**

[0178] Preconcentrates A- L described in Table 12 were prepared as provided in Example 1.

Table 12: Preconcentrates A-L.

Preconcentrate	K85-EE (mg)	Surfactant (mg)	FFA (mg)	Total vol. (mg)	Ratio
A	5002.7	Tween-20 3705.8	Oleic Acid 1307.9	10016.4	49:36:13
B	5004.9	Tween-80 3707.9	Oleic Acid 1302.3	10015.1	49:37:13
C	5003.2	Tween-20 3702.1	Ricioleic acid 1308.1	10013.4	49:36:13
D	5003.5	Tween-80 3703.1	Ricioleic acid 1303.4	10010	49:36:13
E	5000.4	Tween-20 3707.4	Linoleic acid 1305.3	10013.1	49:37:13
F	5001	Tween-80 3706	Linoleic acid 1304.3	10011.3	49:37:13
G	5006.4	Tween-20 3702.1	Erucic acid 1300.2	10008.7	50:36:12
H	5004.3	Tween-80 3704.1	Erucic acid 1303.2	10011.6	49:36:13
I	5002.9	Tween-20 3700.8	α-Linolenic acid 1309.4	10013.1	49:36:13
J	5003.6	Tween-80 3701.6	α-Linolenic acid 1312.1	10017.3	49:36:13

K	5002.9	Tween-20 3700.8	"Pure" EPA-FA+DHA-FA in a ratio close to K85-EE 1309.4	10013.1	49:36:13
L	5002.9	Tween-80 3700.8	"Pure" EPA-FA+DHA-FA in a ratio close to K85-EE 1309.4	10013.1	49:36:13

[0179] From Table 12 above, all preconcentrates appeared clear and homogenous, except for the formulation with erucic acid. As such, the preconcentrates can be mixed in any proportion and these mixtures will still form homogenous and clear preconcentrates.

[0180] Preconcentrates A-L were also screened for compatibility with various solvents. The outcome of this screening is show in Table 13 below. To 500 mg of preconcentrate, approximately 50 mg of each solvent was added. Preconcentrate A was used for all the solvents. Ethanol was tested in all the preconcentrates. The preconcentrates were visually inspected after mixing and again after being stored for 24 hours at room temperature. Under the Preconcentrate heading, a "clear" designation represents a transparent homogenous mixture; an "unclear" designation represents a nonhomogenous mixture, where some turbidity can be observed by visual inspection. The degree of turbidity was not determined.

Table 13: Preconcentrate Compatibility.

Solvent	Preconcentrate A	Preconcentrate B-L
96% Ethanol	Clear	Clear
Benzyl alcohol	Clear	Nd
Propylene glycol	Unclear	Nd
Triacetin	Clear	Nd
PEG 300	Unclear	Nd
Glycerol	Unclear	Nd
1-octadecanol 99%	Clear, but solid	Nd
1-docosanol 98%	Unclear	Nd
Oleyl alcohol 85%	Clear	Nd
1-tetradecanol 97%	Clear	Nd

Nd - Not determined.

[0181] Viscosity can be used as a physical characterization parameter. Viscosity measurements were taken for preconcentrates A-L in triplicate. Generally, the viscosity

showed greater sensitivity for the type of fatty acid than for the type of surfactant. FIG 1 graphically illustrates the viscosity of preconcentrates A-L. Although the viscosity measurements cannot distinguish between Tween 20 versus Tween 80, the viscosity can be impacted by the free fatty acid.

[0182] Preconcentrates A-F, I and J were diluted in gastric and intestinal media to form an emulsion (i.e., SNEDDS/SMEDDS/SEDDS). The composition of the gastric media is shown in Table 14, and the composition of the intestinal media is shown in Table 15.

Table 14: Gastric Media

Gastric Media	
Bile salts, Porcine (mM)	0.08
Lechitin (mM)	0.02
Sodium chloride (mM)	34.2
Pepsin (mg/ml)	0.1
pH	1.6 (adjust with 1 M HCl)
Osmolarity (mOsm/kg)	120

Table 15: Intestinal Media

Intestinal Media	
Bile salts, Porcine Bile extract, Sigma 037K0196 (mM)	5
Phospholipids, LIPOID S PC from LIPOID AG (mM)	1.25
Trizma maleate, Sigma Aldrich , T 3128 (mM)	2
Na^+ (mM)	150

[0183] Particle size was measured using a Malvern Zetasizer (Malvern Instrument, Worcestershire, UK) with particle size measuring range of 0.5 - 6000 nm and Zeta potential of particle range of 3 nm - 10 µm. The particle size was measured in triplicate.

[0184] For the gastric media, the emulsions were prepared by adding 1 ml of gastric media to 50 mg of the preconcentrate. Table 16 below provides the particle size measurements for preconcentrates A-F, I and J in the gastric media. The particle size measurements in gastric media are also graphically illustrated in FIG 2.

Table 16: Particle size measurements for preconcentrates A-F, I and J in gastric media.

Preconcentrates	A	B	C	D	E	F	I	J
Size (nm)	269.6	152.1	216.8	271	271.1	287.1	165	244.3
Standard Deviation	29.63	5.141	26.24	15.94	6.208	36.71	15.87	13.67

[0185] For the intestinal media, the emulsions were prepared by adding the gastric media (100 µl) obtained above to intestinal media (900 µl). Table 17 below provides the particle size measurements for preconcentrates A-F, I and J in the intestinal media. The particle size measurements in intestinal media are also graphically illustrated in FIG 2.

Table 17: Particle size measurements for preconcentrates A-F, I and J in intestinal media.

Preconcentrates	A	B	C	D	E	F	I	J
Size (nm)	245.9	2314	266.7	332.5	233.9	1891	224.3	1788
Standard Deviation	7.465	2438	35.38	26.63	10.48	1936	13.56	930.5

[0186] As shown in FIG 2, intestinal media has a larger impact on the particle size distribution and particularly, preconcentrates comprising Tween 80. That observation has been visualized in FIGs 3-18. FIGs 3-18 show the read out from the Malvern zetasizer for four consecutive measurements on the same sample of each respective preconcentrate. All the preconcentrates give near to unimodal particle size distributions in gastric media, whereas only preconcentrates comprising Tween 20 stays unimodal when transferred to intestinal media.

[0187] **Example 5: Lipolysis and Solubilization**

[0188] Studies were done to analyze the rate of lipolysis (i.e., hydrolysis) and solubilization for different preconcentrates comprising K85EE and different free fatty acids and surfactants. Specifically, four experiments were designed to determine how the amount of surfactant influences the rate and extent of lipolysis and solubilization. The lipolysis was conducted on SMEDDS formulations comprising K85EE.

[0189] Materials

- Bile salts: Porcine Bile extract (Sigma); contains glycine and taurine conjugates of hyodeoxycholic acid and other bile salts.
- Pancreatic lipase, Porcine pancreas (Sigma); contains many enzymes, including amylase, trypsin, lipase, ribonuclease and protease.

- Lechitin: Phospholipids (LIPOID S PC from LIPOID AG)
- Trizma maleate (Sigma Aldrich)
- Tween 20, Molecular Biology Grade (AppliChem Darmstadt), Tween 80 (Fluka)
- α-Linoleic acid (Sigma 60%), Oleic acid (Aldrich 90%)
- K85-EE and K85-FA

[0190] Preconcentrates A-E were prepared as summarized in Table 18.

Table 18: Preconcentrates A-E.

Preconcentrate	Fatty acid oil mixture	Free fatty acid	Surfactant
A	K85EE (400 mg)	oleic acid (100 mg)	Tween 20 (300 mg)
B	K85EE (400 mg)	oleic acid (100 mg)	Tween 20 (75 mg)
C	K85EE (500 mg)	linoleic acid (100 mg)	Tween 80 (200 mg)
D	K85EE (400 mg)	K85FA (100 mg)	Tween 20 (300 mg)
E	K85EE (400 mg)	---	Tween 80 (100 mg)

[0191] Lipolysis general procedure

[0192] The in vitro dynamic lipolysis model developed by Zangenberg et al. (Zangenberg, N.H. et al., *Eur. J. Pharm. Sci.* 14, 237-244, 2001; Zangenberg, N.H., et al., *Eur. J. Pharm. Sci.* 14, 115-122, 2001) was used with slight modifications. The lipolysis was conducted in a thermostated 600 ml jacketed glass vessel in the presence of porcine bile extract, with continuous addition calcium chloride. The lipase source was porcine pancreatin and the hydrolysis was followed by titration with sodium hydroxide solution (1.0 N) using a pH stat (pH 6.5). The initial composition of the lipolysis media is shown in Table 19.

Table 19: Initial composition of lipolysis media.

Substance	Initial Concentration
Pancreatic lipase, Porcine pancreas	800 USP units/ml
Bile salts, Porcine Bile extract	5 mM
Phospholipids, LIPOID S PC from LIPOID AG	1.25 mM
Trizma maleate	2 mM
Na^+	150 mM
K85-EE	5.58 mg/ml

[0193] The final volume in all experiments was 300 ml and the calcium dispensing rate during the experiments was 0.045 mmol/min (0.09 ml/min). In all experiments, the amount of K85-EE added corresponds to 5.58 mg/ml.

[0194] To determine the course of K85-EE lipolysis by HPLC, crude samples were withdrawn and acidified with dilute hydrochloric acid. The concentrations of EPA-EE, DHA-EE, EPA-FA and DHA-FA were determined by HPLC in triplicate. Experiments were performed with LC Agilent Technologies 1200 series at a column temperature of 30°C, mobile phase (A) water (0.1% acetic acid) and (B) MeCN (0.1% acetic acid), with gradient: 0 to 8 minutes, from 70% B to 100% B; 8 to 15 minutes, 100 % B; 16 to 16 minutes: from 100 % B to 70% B, 16 to 20 minutes: 70% B. The flow rate was 0.5 ml/min, UV @ 210 nM, injection volume: 5 µl, and run time: 20 minutes.

[0195] Concentrations of EPA ethyl ester (EPA-EE), DHA ethyl ester (DHA-EE), EPA free acid (EPA-FA), and DHA free acid (DHA-FA) were monitored over time and the rate of lipolysis calculated as shown in Table 20 for comparison with Omacor®.

Table 20: Lipolysis of EPA and DHA ethyl ester in comparison to Omacor® .

	EPA-EE lipolysis (µg/ml/min)	DHA-EE lipolysis (µg/ml/min)	% lipolysis K85EE at t=233 min
Omacor®	1.5	2.3	17
A	2.8	4.5	41
B	2.9	3.9	35
C	3.7	5.0	47
D	3.5	5.0	55
E	3.8	4.3	45

[0196] FIGs 19, 22, 25, 28, 31, and 34 graphically illustrate the disappearance of EPA-EE and DHA-EE and the appearance of EPA-FA and DHA-FA during lipolysis of each respective sample examined. Sample points from 2 minutes to 233 minutes were included in the graphs. In addition, linear regression lines have been included.

[0197] FIGs 20, 23, 26, 29, 32, and 35 provide the percent recovery of EPA + DHA at different time-points for each respective sample examined. Data are given as the sum of EPA-EE, DHA-EE, EPA-FA, and DHA-FA and given as a percentage of theoretical amount 5580 µg/ml.

[0198] FIGs 21, 24, 27, 30, 33, and 36 graphically illustrate the percent lipolysis at different time points for EPA-EE, DHA-EE and total K85EE. Values are calculated relative to the total amount of EPA-EE and DHA-EE determined by HPLC after lipolysis for 2 minutes.

[0199] **Example 6: Fatty Acid Oil Mixtures of Pharmaceutical Compositions/Preconcentrates**

[0200] Fatty acid oil mixtures of pharmaceutical compositions or preconcentrates, wherein the fatty acid oil mixture is a K85-EE composition are presented in Table 21.

Table 21: Fatty acid oil mixture for pharmaceutical compositions/preconcentrates

Fatty acid oil mixture: 1000 mg K85EE fatty acid oil mixture	Minimum Value	Maximum Value
EPAEE + DHAEE	800 mg/g	880 mg/g
EPA EE	430 mg/g	495 mg/g
DHA EE	347 mg/g	403 mg/g
Total omega-3 EE	>90% (w/w)	

EE = ethyl ester

[0201] **Example 7: Tablet Formulations**

[0202] Tablets were prepared by immersing the tablet shown in Table 22 in K85EE oil. The mean liquid loading was 160 mg oil/tablet, corresponding to about 72 v/v%. The tablet can also be prepared without a superdisintegrant.

Table 22: Tablet compositions

Tablet composition	**Example**
Neusilin US	89%
Ac-Di-Sol (croscarmellose sodium) = superdisintegrants	10%
Mg-stearate	1.0%

[0203] **Example 8: Novel K85 Tablet Formulation**

[0204] A tablet formulation is **prepared with the components identified in** Table 23 by immersing a tablet in a K85EE or AGP oil and an oil in free acid form.

Table 23: K83 tablet formulation

K85 or AGP oil loading per tablet	**Minimum**	**Maximum value**
EPA EE and DHA EE	125 mg	600 mg
Free fatty acid oil	2% corresponding to about 2.5 mg	15% corresponding to about 90 mg

[0205] **Example 9: Preparation of SEDDS and SMEDDS**

[0206] The preconcentrate can be prepared by mixing a fatty acid oil mixture together with at least one surfactant and a free fatty acid.

[0207] The preconcentrate can be visually inspected after mixing and again after being stored at 24 hours at room temperature and clear and transparent preconcentrate can be obtained.

[0208] To the preconcentrate can then an aqueous medium be added to form an oil-in-water emulsion. The dispersion rate for the formation of the oil-in-water emulsion can be very fast, less than one minute.

[0209] The microemulsions formed can then be tested regarding hydrolysis, also called lipolysis.

[0210] For example, to determine the course of KE85-EE hydrolysis by HPLC, crude samples can be withdrawn and acidified with dilute hydrochloric acid. The concentrations of EPA- ethyl ester, DHA ethyl ester, EPA-free fatty acid and DHA-free fatty acid can then determined by HPLC.

[0211] All samples withdrawn from a non-homogenous phase and some variability in recovery can be expected, especially at early time points.

Table 24: Initial concentrations of components in the hydrolysis medium.

Substance	**Initial concentration**
Pancreatic lipase, Porcine pancreas, Sigma 095K1149	800 USP units/ml
Bile salts, Porcine Bile extract, Sigma 037K0196	5 mM
Phospholipids, LIPOID S PC from LIPOID AG	1.25 mM
Trizma maleate, Sigma Aldrich , T 3128	2 mM
Na^+	150 mM
KE85-EE	5.58 mg/ml

[0212] An example HPLC analytical method can include the following parameters:

[0213] Use of a LC-MS manufactured by Agilent Technologies and includes a 1200 Series LC and a 6140 Quadropole MS running ChemStation B.04.01 software;

[0214] Column: EclipseXDB C18, 2.1X150 mm, 5µm, Agilent

[0215] Column temperature: 25 °C;

[0216] Mobile Phase: A: water (0.1 %acetic acid), B: MeCN (0.1 % acetic acid);

[0217] Gradient: 0 to 8 min, from 70%B to 100%B, 8 to 15 minutes: 100 % B, from 16 to 16 minutes: from 100 % B to 70% B, 16 to 20 minutes: 70% B;

[0218] Flow rate: 0.5 ml/min;

[0219] UV @ 210 nM;

[0220] Injection volume: 25 µl; and

[0221] Run time: 20 minutes.

[0222] The oil-in-water emulsions can then be further analyzed to determine the particle size of the oil droplets. The particle size can be determined with Malvern Zetasizer (Malvern Instrument, Worcestershire, UK) having particle size measuring range of 0.6 – 6000 nm and Zeta of particle range of 3nm – 10µm.

[0223] Table 25 shows the components that can be included in pharmaceutical compositions and food supplement compositions according to the present disclosure.

Table 25: Sample compositions according to the present disclosure.

	Pharmaceutical composition	**Food Supplement composition**
Fatty Acid Oil Mixture	K85EE, K85TG or AGP103 drug substance	Commercial up-concentrated oil mixture in EE and/or TG form
Surfactant	Tween®20 or Tween®40	Tween®20 or Tween®40
Free Fatty Acid	(EPA-FAand DHA-FA), EPA-FA or DHA-FA	(EPA-FA+DHA-FA), EPA-FA or DHA-FA
Total Oil Mixture 100% by weight	100% by weight	100% by weight

[0224] Further for example, K85EE omega-3 fatty acid oil and the free fatty acid chosen from K85FA having a EPA:DHA -FA ratio more or less equal to the EPA:DHA -EE ratio in K85EE are exemplified in Table 26.

Table 26: Additional compositions according to the present disclosure.

Total oil mixture content [oil:co-surfactant ratio] in SMEDDS/SEDDS Formulations	Fatty Acid Oil Mixture: K85EE	Free Fatty Acid: K85-FA	Free Fatty Acid: EPA-FA or DHA-FA	Free Fatty Acid: EPA and DHA mixture in FA form	Total oil mixture (by weight)
1.)	80-95%		5-20 w%		100 w%
2.)	70-80%		20-30%		100 w%
3.)	50-70%		30-50%		100 w%
4.)	50-60%	40-50%			100 w%

5.)	60-70%	30-40%			100 w%
6.)	70-80%	20-30%			100 w%
7.)	80-95%	5-20%			100 w%
8.)	>80%			<20%	100 w%
9.)	70-80%			20-30%	100 w%
10.)	60-70%			30-40%	100 w%
11.)	50-60%			40-50%	100 w%
12.)	85-95%			5-15% EPA>DHA	100 w%
13.)	80-90%			10-20% EPA>DHA	100 w%
14.)	70-80%			20-30% EPA>DHA	100 w%
15.)	60-70%			30-40% EPA>DHA	100 w%

[0225] Additionally, the total oil mixtures presented above can be mixed with the surfactant Tween®20.

[0226] Further for example, the K85EE mixed fatty acid composition comprises at least 90% omega-3 ethyl ester fatty acids, and wherein the mixed fatty acid composition comprises from about 80% to about 88% eicosapentaenoic acid ethyl ester and docosahexaenoic acid ethyl ester, by weight of the fatty acid composition.

[0227] A collection of ratios between [oil]:[surfactant]:[free fatty acid] (a):b):c)) are illustrated in the table 30. For example, a K85EE or AGP103 oil is used together with a surfactant and a co-surfactant in the [K85EE]:[surfactant]:[free fatty acid] ranges from about 4:2:0.5 to 4:4:2. Thus, the range for the surfactant may be from 2 to 4 and the free fatty acid from 0.5 to 2.

[0228] It is also included herein that the K85EE oil mixture presented in Table 27 above can be replaced by a K85TG oil mixture as well as a commercial omega-3 oil concentrate in ethyl ester and/or triglyceride form.

Table 27: SMEDDS formulations with Tween20, K85EE, EPA-FA or DHA-FA.

	K85EE (mg)	**Tween20 (mg)**	**EPA-FA (mg)**	**DHA-FA (mg)**	**~K85FA (mg)**	**200 mg preconcentrate in 10 ml water**
A	400	400	100			emulsion
B	400	400		100		emulsion

C	400	300	100			emulsion
D	400	300			100	emulsion

[0229] **Example 10: Pharmaceutical Preconcentrate Composition**

[0230] A pharmaceutical preconcentrate composition was prepared by mixing the following components:

[0231] as the fatty acid oil mixture: K85-EE; in an amount of 10.80 g;

[0232] as the surfactant: Tween-20 (Molecular Biology Grade, AppliChem Darmstadt, A4974,0250 lot 5N004174) in an amount of 7.44 g;

[0233] as the at least one fatty acid: EPA-FA in an amount of 1.53 g; and DHA-FA in an amount of 1.24 g.

[0234] With mixing, a transparent homogenous solution was obtained. The density of the formulation was determined to be 1.02 g/ml. The composition was then filled in vials (vial seize = 4ml) each comprising 1.25 x 1670 mg = 2087 mg were prepared, flushed with nitrogen and sealed with parafilm.

[0235] **Example 11: In vivo studies in mini-pig**

[0236] Two different formulations were prepared and sent for in-vivo testing. Formulation 1 was prepared according to Example 12 above by mixing the following components: K85EE, Tween20 EPA-FA and DHA-FA in the specified amounts, and Formulation 2 was OMACOR gelatine capsules.

[0237] The study was performed in 8 male Göttingen SPF minipigs from Ellegaard Göttingen Minipigs ApS. The animals were housed individually in floor pens (1.2 m^2) with sawdust ("Jeluxyl" from Jelu Werk GmbH, Josef Ehrler GmbH & Co KG, Ludwigsmühle, D-73494 Rosenberg, Germany) as bedding.

[0238] Treatment was performed in a cross-over design. The dose was 2 g per animal. The first day of treatment is designated Day 1. Treatment was performed with a wash out period of at least 10 days between each dosing. Blood samples (n=8) were taken post-dosing. Plasma samples were analysed within 2 weeks for total lipid content of EPA and DHA by a validated LC-MS/MS method. The result presented in FIG 37 shows the plasma concentration versus time profile of the total lipid concentration of EPA, supporting supra- bioavailability (e.g., great than 40%) for the K85 SMEDDS formulation. A similar results has also been shown for the time profile of total lipid concentration of DHA (not shown in FIG 37).

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising:

a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and

at least one free fatty acid.

2. The composition according to claim 1, wherein of the at least 75% EPA and DHA of the fatty acid oil mixture, at least 95% is EPA.

3. The composition according to claim 1, wherein of the at least 75% EPA and DHA of the fatty acid oil mixture, at least 95% is DHA.

4. The composition according to claim 1, wherein the fatty acid oil mixture comprises at least 90% omega-3 fatty acids, by weight of the fatty acid oil mixture.

5. The composition according to claim 4, wherein at least one of the omega-3 fatty acids has a *cis* configuration.

6. The composition according to claim 1, wherein the fatty acid oil mixture further comprises at least one other fatty acid other than EPA and DHA in a form chosen from ethyl ester and triglyceride.

7. The composition according to claim 6, wherein the at least one other fatty acid is chosen from α-linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), stearidonic acid (STA), and mixtures thereof.

8. The composition according to claim 6, wherein the at least one other fatty acid is chosen from linoleic acid, α-linolenic acid (ALA), gamma-linolenic acid (GLA), arachidonic acid (AA), osbond acid, and mixtures thereof.

9. The composition according to claim 1, wherein the at least one free fatty acid is a polyunsaturated fatty acid.

10. The composition according to claim 1, wherein the at least one free fatty acid is chosen from EPA, DHA, ALA, HPA, DPA, ETA, ETE, STA, linoleic acid, GLA, AA, osbond acid, oleic acid, ricinoleic acid, erucic acid, and mixtures thereof.

11. The composition according to claim 1, wherein the fatty acid oil mixture is derived from at least one oil chosen from marine oil, algae oil, plant-based oil, and microbial oil.

12. The composition according to claim 11, wherein the marine oil is a purified fish oil.

13. The composition according to claim 1, wherein the fatty acid oil mixture comprises from about 50% to about 95% by weight and the at least one free fatty acid comprises from about 5% to about 50% by weight, each relative to the total weight of the composition.

14. The composition according to claim 1, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:10 to 10:1, from about 1:8 to 8:1, from about 1:6 to 6:1, from about 1:5 to 5:1, from about 1:4 to 4:1, from about 1:3 to 3.1, from about 1.2 to 2:1, from about 1.1 to 2.1, or from about 1.2 to 1.3.

15. The composition according to claim 14, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:2 to 2:1.

16. The composition according to claim 15, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1.2 to 1.3.

17. The composition according to claim 1, wherein the EPA or the DHA of the fatty acid oil mixture, or the EPA and the DHA of the fatty acid oil mixture is in a form of an alpha-substituted fatty acid derivative.

18. The composition according to claim 1, further comprising at least one antioxidant.

19. The composition according to claim 1, further comprising at least one superdisintegrant, and wherein the composition is in a tablet form.

20. The composition according to claim 19, wherein the at least one superdisintegrant is chosen from crosscarmelose, crospovidone, and sodium starch glycolate.

21. The composition according to claim 19, wherein the at least one superdisintegrant comprises from about 1% to about 20% by weight relative to the total weight of the composition.

22. The composition according to claim 1, wherein the fatty acid oil mixture is present in a pharmaceutically-effective amount.

23. The composition according to claim 1, wherein the composition is in the form of a gelatin capsule.

24. The composition according to claim 23, wherein the capsule fill content ranges from about 0.400 g to about 1.300 g.

25. The composition according to claim 24, wherein the capsule fill content ranges from about 0.600 g to about 1.200 g.

26. The composition according to claim 25, wherein the capsule fill content ranges from about 0.800 g to about 1.000 g.

27. A pharmaceutical preconcentrate comprising:

a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride;

at least one free fatty acid; and

at least one surfactant.

28. The preconcentrate according to claim 27, wherein of the at least 75% EPA and DHA of the fatty acid oil mixture, at least 95% is EPA.

29. The preconcentrate according to claim 27, wherein of the at least 75% EPA and DHA of the fatty acid oil mixture, at least 95% is DHA.

30. The preconcentrate according to claim 27, wherein the fatty acid oil mixture comprises at least 90% omega-3 fatty acids, by weight of the fatty acid oil mixture.

31. The preconcentrate according to claim 30, wherein at least one of the omega-3 fatty acids has a *cis* configuration.

32. The preconcentrate according to claim 27, wherein the fatty acid oil mixture further comprises at least one other fatty acid other than EPA and DHA in a form chosen from ethyl ester and triglyceride.

33. The preconcentrate according to claim 32, wherein the at least one other fatty acid is chosen from α-linolenic acid (ALA), heneicosapentaenoic acid (HPA),

docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), stearidonic acid (STA), and mixtures thereof.

34. The preconcentrate according to claim 32, wherein the at least one other fatty acid is chosen from linoleic acid, α-linolenic acid (ALA), gamma-linolenic acid (GLA), arachidonic acid (AA), osbond acid, and mixtures thereof.

35. The preconcentrate according to claim 27, wherein the at least one free fatty acid is a polyunsaturated fatty acid.

36. The preconcentrate according to claim 27, wherein the at least one free fatty acid is chosen from EPA, DHA, ALA, HPA, DPA, ETA, ETE, STA, linoleic acid, GLA, AA, osbond acid, oleic acid, ricinoleic acid, erucic acid, and mixtures thereof.

37. The preconcentrate according to claim 27, wherein the fatty acid oil mixture is derived from at least one oil chosen from marine oil, algae oil, plant-based oil, and microbial oil.

38. The preconcentrate according to claim 37, wherein the marine oil is a purified fish oil.

39. The preconcentrate according to claim 27, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:10 to 10:1, from about 1:8 to 8:1, from about 1:6 to 6:1, from about 1:5 to 5:1, from about 1:4 to 4:1, from about 1:3 to 3.1, from about 1.2 to 2:1, from about 1.1 to 2.1, or from about 1.2 to 1.3.

40. The preconcentrate according to claim 39, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:2 to 2:1.

41. The preconcentrate according to claim 40, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1.2 to 1.3.

42. The preconcentrate according to claim 1, wherein the EPA or the DHA of the fatty acid oil mixture, or the EPA and the DHA of the fatty acid oil mixture is in a form of an alpha-substituted fatty acid derivative.

43. The preconcentrate according to claim 27, further comprising at least one antioxidant.

44. The preconcentrate according to claim 27, wherein the fatty acid oil mixture is present in a pharmaceutically-effective amount.

45. The preconcentrate according to claim 27, wherein the preconcentrate is in the form of a gelatin capsule.

46. The preconcentrate according to claim 45, wherein the capsule fill content ranges from about 0.400 g to about 1.300 g.

47. The preconcentrate according to claim 46, wherein the capsule fill content ranges from about 0.600 g to about 1.200 g.

48. The preconcentrate according to claim 47, wherein the capsule fill content ranges from about 0.800 g to about 1.000 g.

49. The preconcentrate according to claim 27, wherein the at least one surfactant is chosen from anionic, nonionic, cationic, zwitterionic surfactants, and mixtures thereof.

50. The preconcentrate according to claim 49, wherein the anionic surfactants are chosen from salts of perfluorocarboxylic acids and perfluorosulphonic acid, alkyl sulphate salts, sulphate ethers, alkyl benzene sulphonate salts, and mixtures thereof.

51. The preconcentrate according to claim 49, wherein the nonionic surfactants are chosen from diacetyl monoglycerides, diethylene glycol monopalmitostearates, ethylene glycol monopalmitostearates, glyceryl behenates, glyceryl distearates, glyceryl monolinoleates, glyceryl mono-oleates, glyceryl monostearates, macrogol cetostearyl ethesr, macrogol 15 hydroxystearates, macrogol lauril ethers, macrogol monomethyl ethers, macrogol oleyl ethers, macrogol stearas, menfegol, mono and diglycerides, nonoxinols, octoxinols, polyoxamers, polyoxamer 188, polyoxamer 407, polyoxyl castor oils, polyoxyl hydrogenated castor oils, propylene glycol diacetates, propylene glycol laureates, propylene glycol monopalmitostearates, quillaia, sorbitan esters, sucrose esters, and mixtures thereof.

52. The preconcentrate according to claim 49, wherein the nonionic surfactants are chosen from nonionic copolymers comprised of a central hydrophobic polymer of polyoxypropylene(poly(propylene oxide)) with a hydrophilic polymer of at least one of polyethylene(poly(ethylene oxide)), polyethylene ethers, sorbitan esters, polyoxyethylene fatty acid esters, polyethylated castor oil, and mixtures thereof.

53. The preconcentrate according to claim 52, wherein the nonionic surfactants are chosen from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, and mixtures thereof.

54. The preconcentrate according to claim 49, wherein the cationic surfactants are chosen from quaternary ammonium compounds, cetylpyridinium chlorides, benzethonium chlorides, cetyl trimethylammonium bromides, and mixtures thereof.

55. The preconcentrate according to claim 49, wherein the zwitterionic surfactants are chosen from dodecyl betaines, coco amphoglycinates, cocamidopropyl betaines, and mixtures thereof.

56. The preconcentrate according to claim 27, wherein the at least one surfactant is a phospholipid, derivative thereof, analogue thereof, or any mixture thereof.

57. The preconcentrate according to claim 56, wherein the phospholipid, derivative thereof, or analogue thereof is chosen from natural, synthetic, semisynthetic phospholipids, and mixtures thereof.

58. The preconcentrate according to claim 57, wherein the phospholipid or derivative or analogue thereof is chosen from phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, and mixtures thereof.

59. The preconcentrate according to claim 27, wherein the ratio of fatty acid oil mixture:surfactant ranges from about 1:1 to about 10:1, from about 1:1 to about 8:1, from about 1:1 to about 6:1. from about 1:1 to about 4:1, or from about 1:1 to about 3:1.

60. The preconcentrate according to claim 27, wherein the at least one surfactant comprises from about 5% to about 55%, from about 10% to about 30%, or from about 10% to about 25%, by weight relative to the total weight of the preconcentrate.

61. The preconcentrate according to claim 60, wherein the at least one surfactant comprises about 20%, by weight relative to the total weight of the preconcentrate.

62. The preconcentrate according to claim 27, further comprising at least one pharmaceutically-acceptable solvent.

63. The preconcentrate according to claim 61, wherein the at least one pharmaceutically-acceptable solvent is chosen from lower alcohols and polyols.

64. A pharmaceutical preconcentrate comprising:

a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form;

at least one free fatty acid comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the at least one free fatty acid, wherein the EPA and DHA are in free fatty acid form; and

at least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof.

65. A pharmaceutical preconcentrate comprising:

from about 45% to about 55% by weight, relative to the weight of the preconcentrate, of a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride;

from about 5% to about 15% of at least one free fatty acid, by weight relative to the weight of the preconcentrate; and

from about 30% to about 40% of at least one surfactant, by weight relative to the weight of the preconcentrate.

66. A pharmaceutical preconcentrate comprising:

from about 55% to about 65% by weight, relative to the weight of the preconcentrate, of a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride;

from about 5% to about 15% of at least one free fatty acid, by weight relative to the weight of the preconcentrate; and

from about 20% to about 30% of at least one surfactant, by weight relative to the weight of the preconcentrate.

67. The preconcentrate according to claim 65 or 66, wherein the at least one free fatty acid is chosen from oleic acid, ricioleic acid, linoleic acid, α-linolenic acid (ALA), gamma-linolenic acid (GLA) and erucic acid and the at least one surfactant is chosen from polysorbate 20 and polysorbate 80.

68. A pharmaceutical preconcentrate comprising:

a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form;

at least one free fatty acid comprising oleic acid; and

at least one surfactant chosen from polysorbate 20 and polysorbate 80.

69. A self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) comprising a pharmaceutical preconcentrate comprising:

a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride;

at least one free fatty acid; and

at least one surfactant;

wherein the preconcentrate forms an emulsion in an aqueous solution.

70. The system according to claim 69, wherein the fatty acid oil mixture comprises at least 90% omega-3 fatty acids, by weight of the fatty acid oil mixture.

71. The system according to claim 70, wherein at least one of the omega-3 fatty acids has a *cis* configuration.

72. The system according to claim 69, wherein the fatty acid oil mixture further comprises at least one other fatty acid other than EPA and DHA in a form chosen from ethyl ester and triglyceride.

73. The system according to claim 72, wherein the at least one other fatty acid is chosen from α-linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), stearidonic acid (STA), and mixtures thereof.

74. The system according to claim 72, wherein the at least one other fatty acid is chosen from linoleic acid, α-linolenic acid (ALA), gamma-linolenic acid (GLA), arachidonic acid (AA), osbond acid, and mixtures thereof.

75. The system according to claim 69, wherein the at least one free fatty acid is a polyunsaturated fatty acid.

76. The system according to claim 69, wherein the at least one free fatty acid is chosen from EPA, DHA, ALA, HPA, DPA, ETA, ETE, STA, linoleic acid, GLA, AA, osbond acid, oleic acid, ricinoleic acid, erucic acid, and mixtures thereof.

77. The system according to claim 69, wherein the fatty acid oil mixture is derived from at least one oil chosen from marine oil, algae oil, plant-based oil, and microbial oil.

78. The system according to claim 77, wherein the marine oil is a purified fish oil.

79. The system according to claim 69, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:10 to 10:1, from about 1:8 to 8:1, from about 1:6 to 6:1, from about 1:5 to 5:1, from about 1:4 to 4:1, from about 1:3 to 3.1, from about 1.2 to 2:1, from about 1.1 to 2.1, or from about 1.2 to 1.3.

80. The system according to claim 79, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:2 to 2:1.

81. The system according to claim 80, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1.2 to 1.3.

82. The system according to claim 69, wherein the EPA or the DHA of the fatty acid oil mixture, or the EPA and the DHA of the fatty acid oil mixture is in a form of an alpha-substituted fatty acid derivative.

83. The system according to claim 69, wherein the preconcentrate further comprises at least one antioxidant.

84. The system according to claim 69, wherein the fatty acid oil mixture is present in a pharmaceutically-effective amount.

85. The system according to claim 69, wherein the system is in the form of a gelatin capsule.

86. The system according to claim 69, wherein the capsule fill content ranges from about 0.400 g to about 1.300 g.

87. The system according to claim 86, wherein the capsule fill content ranges from about 0.600 g to about 1.200 g.

88. The system according to claim 87, wherein the capsule fill content ranges from about 0.800 g to about 1.000 g.

89. The system according to claim 69, wherein the at least one surfactant is chosen from anionic, nonionic, cationic, zwitterionic surfactants, and mixtures thereof.

90. The system according to claim 89, wherein the anionic surfactants are chosen from salts of perfluorocarboxylic acids and perfluorosulphonic acid, alkyl sulphate salts, sulphate ethers, alkyl benzene sulphonate salts, and mixtures thereof.

91. The system according to claim 89, wherein the nonionic surfactants are chosen from diacetyl monoglycerides, diethylene glycol monopalmitostearates, ethylene glycol monopalmitostearates, glyceryl behenates, glyceryl distearates, glyceryl monolinoleates, glyceryl mono-oleates, glyceryl monostearates, macrogol cetostearyl ethesr, macrogol 15 hydroxystearates, macrogol lauril ethers, macrogol monomethyl ethers, macrogol oleyl ethers, macrogol stearas, menfegol, mono and diglycerides, nonoxinols, octoxinols, polyoxamers, polyoxamer 188, polyoxamer 407, polyoxyl castor oils, polyoxyl hydrogenated castor oils, propylene glycol diacetates, propylene glycol laureates, propylene glycol monopalmitostearates, quillaia, sorbitan esters, sucrose esters, and mixtures thereof.

92. The system according to claim 89, wherein the nonionic surfactants are chosen from nonionic copolymers comprised of a central hydrophobic polymer of polyoxypropylene(poly(propylene oxide)) with a hydrophilic polymer of at least one of polyethylene(poly(ethylene oxide)), polyethylene ethers, sorbitan esters, polyoxyethylene fatty acid esters, polyethylated castor oil, and mixtures thereof.

93. The system according to claim 92, wherein the nonionic surfactants are chosen from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, and mixtures thereof.

94. The system according to claim 89, wherein the cationic surfactants are chosen from quaternary ammonium compounds, cetylpyridinium chlorides, benzethonium chlorides, cetyl trimethylammonium bromides, and mixtures thereof.

95. The system according to claim 89, wherein the zwitterionic surfactants are chosen from dodecyl betaines, coco amphoglycinates, cocamidopropyl betaines, and mixtures thereof.

96. The system according to claim 69, wherein the at least one surfactant is a phospholipid, derivative thereof, analogue thereof, or any mixture thereof.

97. The system according to claim 96, wherein the phospholipid, derivative thereof, or analogue thereof is chosen from natural, synthetic, semisynthetic phospholipids, and mixtures thereof.

98. The system according to claim 97, wherein the phospholipid or derivative or analogue thereof is chosen from phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, and mixtures thereof.

99. The system according to claim 69, wherein the ratio of fatty acid oil mixture:surfactant ranges from about 1:1 to about 10:1, from about 1:1 to about 8:1, from about 1:1 to about 6:1, from about 1:1 to about 4:1, or from about 1:1 to about 3:1.

100. The system according to claim 69, wherein the at least one surfactant comprises from about 5% to about 55%, from about 10% to about 30%, or from about 10% to about 25%, by weight relative to the total weight of the system.

101. The system according to claim 100, wherein the at least one surfactant comprises about 20%, by weight relative to the total weight of the system.

102. The system according to claim 69, wherein the preconcentrate further comprises at least one pharmaceutically-acceptable solvent.

103. The system according to claim 102, wherein the at least one pharmaceutically-acceptable solvent is chosen from lower alcohols and polyols.

104. The system according to claim 69, wherein the particle size of the emulsion ranges from about 150 nm to about 350 nm.

105. A method of treating at least one health problem in a subject in need thereof comprising administering to the subject a pharmaceutical composition comprising:

a pharmaceutically-effective amount of a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and

at least one free fatty acid;

wherein the at least one health problem is chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

106. The method according to claim 105, wherein the at least one health problem is chosen from mixed dyslipidemia, dyslipidemia, hypertriglyceridemia, hypercholesterolemia, heart failure, and post myocardial infarction.

107. The method according to claim 106, wherein said method treats elevated triglyceride levels, non-HDL cholesterol levels, LDL cholesterol levels and/or VLDL cholesterol levels.

108. The method according to claim 107, wherein in the subject with elevated triglyceride levels, said method reduces triglyceride levels from about 40% to about 70% or from about 40% to about 60%.

109. The method according to claim 105, wherein the fatty acid oil mixture comprises at least 90% omega-3 fatty acids, by weight of the fatty acid oil mixture.

110. The method according to claim 109, wherein at least one of the omega-3 fatty acids has a *cis* configuration.

111. The method according to claim 105, wherein the fatty acid oil mixture further comprises at least one other fatty acid other than EPA and DHA in a form chosen from ethyl ester and triglyceride.

112. The method according to claim 111, wherein the at least one other fatty acid is chosen from α-linolenic acid (ALA), heneicosapentaenoic acid (HPA), docosapentaenoic acid (DPA), eicosatetraenoic acid (ETA), eicosatrienoic acid (ETE), stearidonic acid (STA), and mixtures thereof.

113. The method according to claim 111, wherein the at least one other fatty acid is chosen from linoleic acid, α-linolenic acid (ALA), gamma-linolenic acid (GLA), arachidonic acid (AA), osbond acid, and mixtures thereof.

114. The method according to claim 105, wherein the at least one free fatty acid is a polyunsaturated fatty acid.

115. The method according to claim 105, wherein the at least one free fatty acid is chosen from EPA, DHA, ALA, HPA, DPA, ETA, ETE, STA, linoleic acid, GLA, AA, osbond acid, oleic acid, ricinoleic acid, erucic acid, and mixtures thereof.

116. The method according to claim 105, wherein the fatty acid oil mixture is derived from at least one oil chosen from marine oil, algae oil, plant-based oil, and microbial oil.

117. The method according to claim 116, wherein the marine oil is a purified fish oil.

118. The method according to claim 105, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:10 to 10:1, from about 1:8 to 8:1, from about 1:6 to 6:1, from about 1:5 to 5:1, from about 1:4 to 4:1, from about 1:3 to 3.1, from about 1.2 to 2:1, from about 1.1 to 2.1, or from about 1.2 to 1.3.

119. The method according to claim 118, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:2 to 2:1.

120. The method according to claim 119, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1.2 to 1.3.

121. The method according to claim 105, wherein the EPA or the DHA of the fatty acid oil mixture, or the EPA and the DHA of the fatty acid oil mixture is in a form of an alpha-substituted fatty acid derivative.

122. The method according to claim 105, wherein the composition further comprises at least one antioxidant.

123. The method according to claim 105, wherein the composition further comprises at least one superdisintegrant, and wherein the composition is in a tablet form.

124. The method according to claim 123, wherein the at least one superdisintegrant is chosen from crosscarmelose, crospovidone, and sodium starch glycolate.

125. The method according to claim 124, wherein the at least one superdisintegrant comprises from about 1% to about 20%, by weight relative to the total weight of the pharmaceutical composition.

126. The method according to claim 105, wherein the composition is in the form of a gelatin capsule.

127. The method according to claim 126, wherein the capsule fill content ranges from about 0.400 g to about 1.300 g.

128. The method according to claim 127, wherein the capsule fill content ranges from about 0.600 g to about 1.200 g.

129. The method according to claim 128, wherein the capsule fill content ranges from about 0.800 g to about 1.000 g.

130. The method according to claim 105, wherein the composition is administered once, twice, or three times per day.

131. The method according to claim 105, wherein the composition further comprises at least one surfactant to form a pharmaceutical preconcentrate.

132. The method according to claim 131, wherein the at least one surfactant is chosen from anionic, nonionic, cationic, zwitterionic surfactants, and mixtures thereof.

133. The method according to claim 132, wherein the anionic surfactants are chosen from salts of perfluorocarboxylic acids and perfluorosulphonic acid, alkyl sulphate salts, sulphate ethers, alkyl benzene sulphonate salts, and mixtures thereof.

134. The method according to claim 132, wherein the nonionic surfactants are chosen from diacetyl monoglycerides, diethylene glycol monopalmitostearates, ethylene glycol monopalmitostearates, glyceryl behenates, glyceryl distearates, glyceryl monolinoleates, glyceryl mono-oleates, glyceryl monostearates, macrogol cetostearyl ethesr, macrogol 15 hydroxystearates, macrogol lauril ethers, macrogol monomethyl ethers, macrogol oleyl ethers, macrogol stearas, menfegol, mono and diglycerides, nonoxinols, octoxinols, polyoxamers, polyoxamer 188, polyoxamer 407, polyoxyl castor oils, polyoxyl hydrogenated castor oils, propylene glycol diacetates, propylene glycol laureates, propylene glycol monopalmitostearates, quillaia, sorbitan esters, sucrose esters, and mixtures thereof.

135. The method according to claim 132, wherein the nonionic surfactants are chosen from nonionic copolymers comprised of a central hydrophobic polymer of polyoxypropylene(poly(propylene oxide)) with a hydrophilic polymer of at least one of polyethylene(poly(ethylene oxide)), polyethylene ethers, sorbitan esters, polyoxyethylene fatty acid esters, polyethylated castor oil, and mixtures thereof.

136. The method according to claim 135, wherein the nonionic surfactants are chosen from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, and mixtures thereof.

137. The method according to claim 132, wherein the cationic surfactants are chosen from quaternary ammonium compounds, cetylpyridinium chlorides, benzethonium chlorides, cetyl trimethylammonium bromides, and mixtures thereof.

138. The method according to claim 132, wherein the zwitterionic surfactants are chosen from dodecyl betaines, coco amphoglycinates, cocamidopropyl betaines, and mixtures thereof.

139. The method according to claim 131, wherein the at least one surfactant is a phospholipid, derivative thereof, analogue thereof, or any mixture thereof.

140. The method according to claim 139, wherein the phospholipid, derivative thereof, or analogue thereof is chosen from natural, synthetic, semisynthetic phospholipids, and mixtures thereof.

141. The method according to claim 140, wherein the phospholipid or derivative or analogue thereof is chosen from phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, and mixtures thereof.

142. The method according to claim 131, wherein the preconcentrate forms a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) in an aqueous solution.

143. A food supplement or nutritional supplement composition comprising:

a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and

at least one free fatty acid.

144. The composition according to claim 143, wherein the fatty acid oil mixture comprises from about 35% to about 75% EPA and DHA, by weight of the fatty acid oil mixture, from about 40% to about 70% EPA and DHA, by weight of the fatty acid oil mixture, from about 40% to about 65% EPA and DHA, by weight of the fatty acid oil mixture, from about 40% to about 60% EPA and DHA, by weight of the fatty acid oil mixture, from about 40% to about 55% EPA and DHA, by weight of the fatty acid oil mixture, or from about 50% to about 55% EPA and DHA, by weight of the fatty acid oil mixture.

145. The composition according to claim 143, wherein the fatty acid oil mixture is derived from at least one oil chosen from marine oil, algae oil, plant-based oil, and microbial oil.

146. The composition according to claim 145, wherein the marine oil is a purified fish oil.

147. The composition according to claim 143, wherein the EPA:DHA weight ratio of the fatty acid oil mixture ranges from about 1:10 to 10:1, from about 1:8 to 8:1, from about 1:6 to 6:1, from about 1:5 to 5:1, from about 1:4 to 4:1, from about 1:3 to 3.1, from about 1.2 to 2:1, from about 1.1 to 2.1, or from about 1.2 to 1.3.

148. The composition according to claim 143, wherein the at least one free fatty acid is a polyunsaturated fatty acid.

149. The composition according to claim 143, wherein the at least one free fatty acid is chosen from EPA, DHA, ALA, HPA, DPA, ETA, ETE, STA, linoleic acid, GLA, AA, osbond acid, oleic acid, ricinoleic acid, erucic acid, and mixtures thereof.

150. The composition according to claim 143, further comprising at least one antioxidant.

151. The composition according to claim 143, further comprising at least one superdisintegrant and wherein the composition is a tablet form.

152. The composition according to claim 151, wherein the at least one superdisintegrant is chosen from crosscarmelose, crospovidone, and sodium starch glycolate.

153. The composition according to claim 151, wherein the at least one superdisintegrant comprises from about 1% to about 20%, by weight relative to the total weight of the composition.

154. The composition according to claim 143, wherein the composition is in the form of a gelatin capsule.

155. The composition according to claim 154, wherein the capsule fill content ranges from about 0.400 g to about 1.300 g.

156. The composition according to claim 155, wherein the capsule fill content ranges from about 0.600 g to about 1.200 g.

157. The composition according to claim 156, wherein the capsule fill content ranges from about 0.800 g to about 1.000 g.

158. A food supplement or nutritional supplement composition comprising:

a fatty acid oil mixture comprising from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from methyl ester, ethyl ester, and triglyceride; and

at least one free fatty acid.

159. The composition according to claim 143, further comprising at least one surfactant to form a supplement preconcentrate.

160. The preconcentrate according to claim 159, wherein the at least one surfactant is chosen from anionic, nonionic, cationic, zwitterionic surfactants, and mixtures thereof.

161. The preconcentrate according to claim 160, wherein the anionic surfactants are chosen from salts of perfluorocarboxylic acids and perfluorosulphonic acid, alkyl sulphate salts, sulphate ethers, alkyl benzene sulphonate salts, and mixtures thereof.

162. The preconcentrate according to claim 160, wherein the nonionic surfactants are chosen from diacetyl monoglycerides, diethylene glycol monopalmitostearates, ethylene glycol monopalmitostearates, glyceryl behenates, glyceryl distearates, glyceryl monolinoleates, glyceryl mono-oleates, glyceryl monostearates, macrogol cetostearyl ethesr, macrogol 15 hydroxystearates, macrogol lauril ethers, macrogol monomethyl ethers, macrogol oleyl ethers, macrogol stearas, menfegol, mono and diglycerides, nonoxinols, octoxinols, polyoxamers, polyoxamer 188, polyoxamer 407, polyoxyl castor oils, polyoxyl hydrogenated castor oils, propylene glycol diacetates, propylene glycol laureates, propylene glycol monopalmitostearates, quillaia, sorbitan esters, sucrose esters, and mixtures thereof.

163. The preconcentrate according to claim 160, wherein the nonionic surfactants are chosen from nonionic copolymers comprised of a central hydrophobic polymer of polyoxypropylene(poly(propylene oxide)) with a hydrophilic polymer of at least one of polyethylene(poly(ethylene oxide)), polyethylene ethers, sorbitan esters, polyoxyethylene fatty acid esters, polyethylated castor oil, and mixtures thereof.

164. The preconcentrate according to claim 163, wherein the nonionic surfactants are chosen from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, and mixtures thereof.

165. The preconcentrate according to claim 160, wherein the cationic surfactants are chosen from quaternary ammonium compounds, cetylpyridinium chlorides, benzethonium chlorides, cetyl trimethylammonium bromides, and mixtures thereof.

166. The preconcentrate according to claim 160, wherein the zwitterionic surfactants are chosen from dodecyl betaines, coco amphoglycinates, cocamidopropyl betaines, and mixtures thereof.

167. The preconcentrate according to claim 159, wherein the at least one surfactant is a phospholipid, derivative thereof, analogue thereof, or any mixture thereof.

168. The preconcentrate according to claim 167, wherein the phospholipid, derivative thereof, or analogue thereof is chosen from natural, synthetic, semisynthetic phospholipids, and mixtures thereof.

169. The preconcentrate according to claim 168, wherein the phospholipid or derivative or analogue thereof is chosen from phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, and mixtures thereof.

170. The preconcentrate according to claim 159, further comprising at least one pharmaceutically-acceptable solvent.

171. The preconcentrate according to claim 170, wherein the at least one pharmaceutically-acceptable solvent is chosen from lower alcohols and polyols.

172. The preconcentrate according to claim 159, wherein the preconcentrate forms a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) in an aqueous solution.

173. A method for enhancing at least one parameter chosen from hydrolysis, solubility, bioavailability, absorption, and combinations thereof of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) comprising combining:

a fatty acid oil mixture comprising EPA and DHA in a form chosen from ethyl ester and triglyceride; and

at least one free fatty acid.

174. The method according to claim [0162], wherein the fatty acid oil mixture comprises at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture.

175. The method according to claim [0162], wherein the fatty acid oil mixture comprises from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture.

176. A method for enhancing at least one parameter chosen from hydrolysis, solubility, bioavailability, absorption, and combinations thereof of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) comprising combining:

a fatty acid oil mixture comprising EPA and DHA in a form chosen from ethyl ester and triglyceride;

at least one free fatty acid; and

at least one surfactant;

wherein the fatty acid oil mixture, that at least one free fatty acid, and the at least one surfactant form a preconcentrate.

177. The method according to claim 176, wherein the fatty acid oil mixture comprises at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture.

178. The method according to claim 176, wherein the fatty acid oil mixture comprises from about 25% to about 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture.

179. The system according to claim 176, wherein the at least one surfactant is chosen from anionic, nonionic, cationic, zwitterionic surfactants, and mixtures thereof.

180. The system according to claim 179, wherein the anionic surfactants are chosen from salts of perfluorocarboxylic acids and perfluorosulphonic acid, alkyl sulphate salts, sulphate ethers, alkyl benzene sulphonate salts, and mixtures thereof.

181. The system according to claim 179, wherein the nonionic surfactants are chosen from diacetyl monoglycerides, diethylene glycol monopalmitostearates, ethylene glycol monopalmitostearates, glyceryl behenates, glyceryl distearates, glyceryl monolinoleates, glyceryl mono-oleates, glyceryl monostearates, macrogol cetostearyl ethesr, macrogol 15 hydroxystearates, macrogol lauril ethers, macrogol monomethyl ethers, macrogol oleyl ethers, macrogol stearas, menfegol, mono and diglycerides,

nonoxinols, octoxinols, polyoxamers, polyoxamer 188, polyoxamer 407, polyoxyl castor oils, polyoxyl hydrogenated castor oils, propylene glycol diacetates, propylene glycol laureates, propylene glycol monopalmitostearates, quillaia, sorbitan esters, sucrose esters, and mixtures thereof.

182. The system according to claim 179, wherein the nonionic surfactants are chosen from nonionic copolymers comprised of a central hydrophobic polymer of polyoxypropylene(poly(propylene oxide)) with a hydrophilic polymer of at least one of polyethylene(poly(ethylene oxide)), polyethylene ethers, sorbitan esters, polyoxyethylene fatty acid esters, polyethylated castor oil, and mixtures thereof.

183. The system according to claim 182, wherein the nonionic surfactants are chosen from polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, and mixtures thereof.

184. The system according to claim 179, wherein the cationic surfactants are chosen from quaternary ammonium compounds, cetylpyridinium chlorides, benzethonium chlorides, cetyl trimethylammonium bromides, and mixtures thereof.

185. The system according to claim 179, wherein the zwitterionic surfactants are chosen from dodecyl betaines, coco amphoglycinates, cocamidopropyl betaines, and mixtures thereof.

186. The system according to claim 176, wherein the at least one surfactant is a phospholipid, derivative thereof, analogue thereof, or any mixture thereof.

187. The system according to claim 186, wherein the phospholipid, derivative thereof, or analogue thereof is chosen from natural, synthetic, semisynthetic phospholipids, and mixtures thereof.

188. The system according to claim 187, wherein the phospholipid or derivative or analogue thereof is chosen from phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, and mixtures thereof.

189. The system according to claim 177, wherein the preconcentrate comprises:

a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form;

at least one free fatty acid comprising oleic acid; and

at least one surfactant chosen from polysorbate 20 and polysorbate 80.

190. The system according to claim 177, wherein the preconcentrate comprises:

a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form;

at least one free fatty acid comprising linoleic acid; and

at least one surfactant chosen from polysorbate 20 and polysorbate 80.

191. The system according to claim 177, wherein the preconcentrate comprises:

a fatty acid oil mixture comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in ethyl ester form;

at least one free fatty acid comprising from about 80% to about 88% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the at least one free fatty acid, wherein the EPA and DHA are in free fatty acid form; and

at least one surfactant chosen from polysorbate 20, polysorbate 80, and mixtures thereof.

192. The method according to claim 176, wherein the preconcentrate forms a self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) in an aqueous solution.

193. The method according to claim 192, wherein the system comprises an emulsion with a particle size ranging from about 150 nm to about 350 nm.

194. A pharmaceutical composition comprising a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid for the treatment of at least one health problem chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

195. A pharmaceutical preconcentrate comprising a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant for the treatment of at least one health problem chosen from irregular plasma lipid levels, cardiovascular

functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

196. A self-nanoemulsifying drug delivery system (SNEDDS), self-microemulsifying drug delivery system (SMEDDS), or self-emulsifying drug delivery system (SEDDS) comprising a pharmaceutical preconcentrate comprising: a fatty acid oil mixture comprising at least 75% eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; at least one free fatty acid; and at least one surfactant; wherein the preconcentrate forms an emulsion in an aqueous solution for the treatment of at least one health problem chosen from irregular plasma lipid levels, cardiovascular functions, immune functions, visual functions, insulin action, neuronal development, heart failure, and post myocardial infarction.

FIG. 1

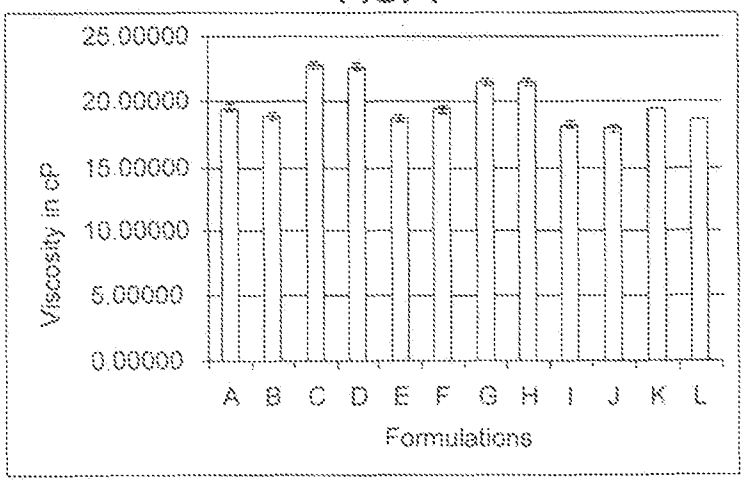

25.00000
20.00000
15.00000
10.00000
5.00000
0.00000
Viscosity in cP
A B C D E F G H I J K L
Formulations

FIG. 2

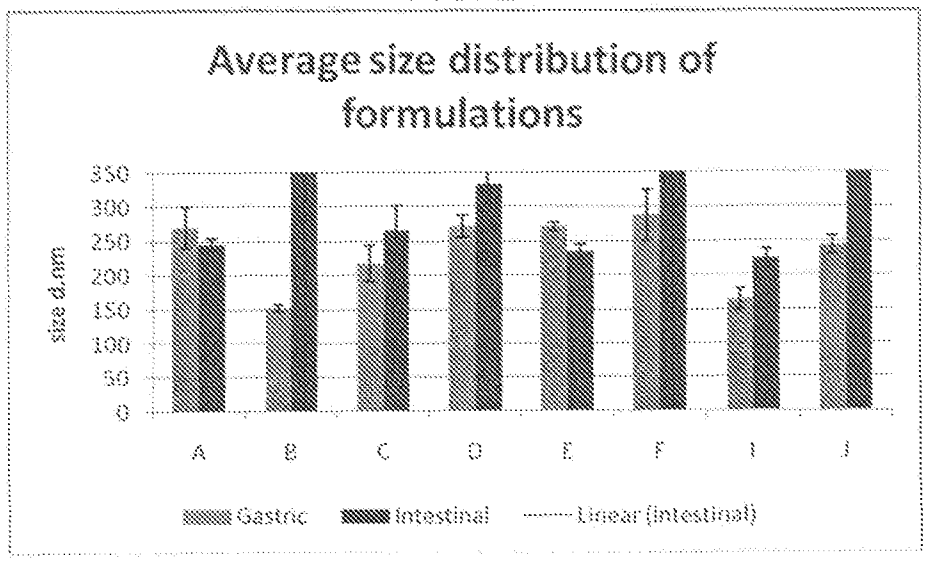

Average size distribution of formulations
350
300
250
200
150
100
50
0
size d.nm
A B C D E F I J
Gastric
Intestinal
Linear (Intestinal)

FIG. 3

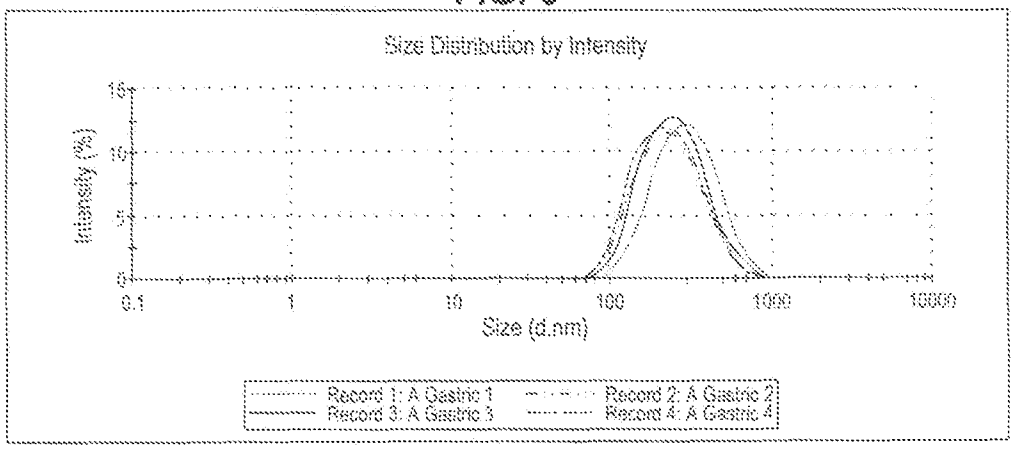

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 1: A Gastric 1
Record 2: A Gastric 2
Record 3: A Gastric 3
Record 4: A Gastric 4

FIG. 4

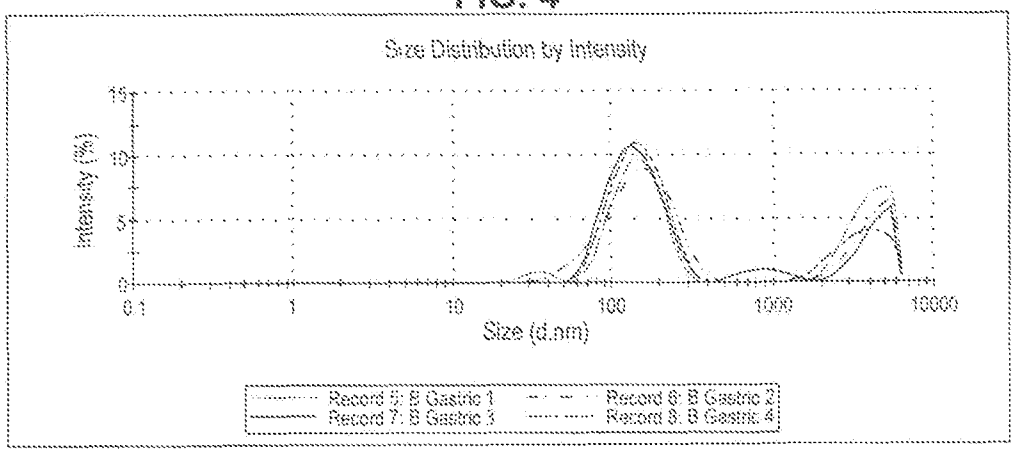

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 5: B Gastric 1
Record 6: B Gastric 2
Record 7: B Gastric 3
Record 8: B Gastric 4

FIG. 5

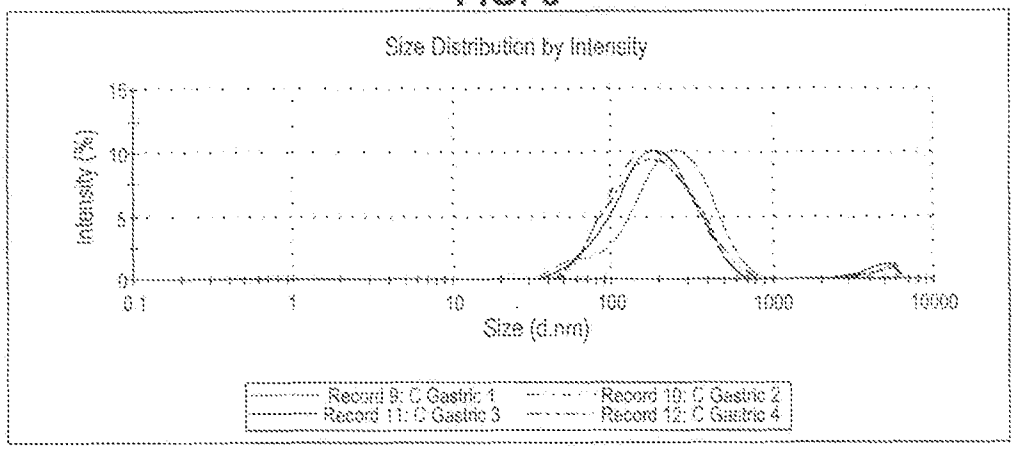

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 9: C Gastric 1
Record 10: C Gastric 2
Record 11: C Gastric 3
Record 12: C Gastric 4

FIG. 6

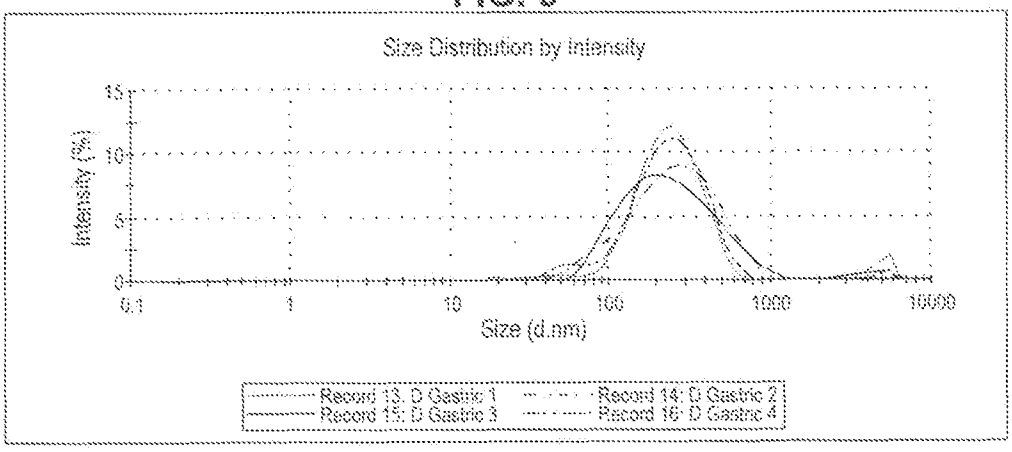

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 13: D Gastric 1
Record 14: D Gastric 2
Record 15: D Gastric 3
Record 16: D Gastric 4

FIG. 7

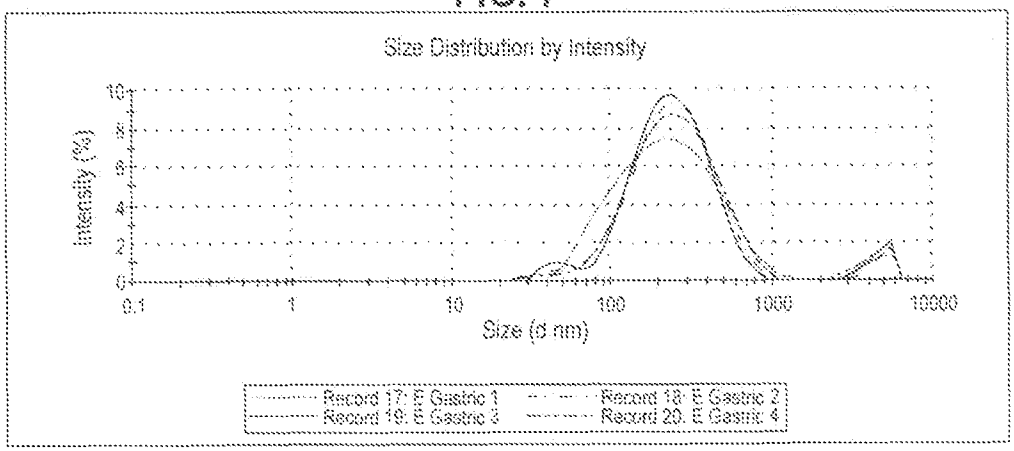

Size Distribution by Intensity
Intensity (%)
0
2
4
6
8
10
0.1
1
10
100
1000
10000
Size (d.nm)
Record 17: E Gastric 1
Record 18: E Gastric 2
Record 19: E Gastric 3
Record 20: E Gastric 4

FIG. 8

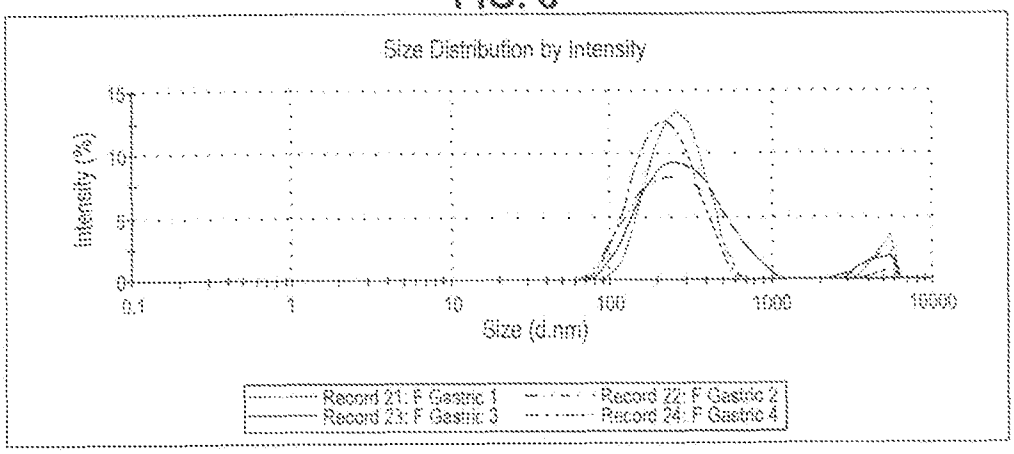

Size Distribution by Intensity
Intensity (%)
0
5
10
15
0.1
1
10
100
1000
10000
Size (d.nm)
Record 21: F Gastric 1
Record 22: F Gastric 2
Record 23: F Gastric 3
Record 24: F Gastric 4

FIG. 9

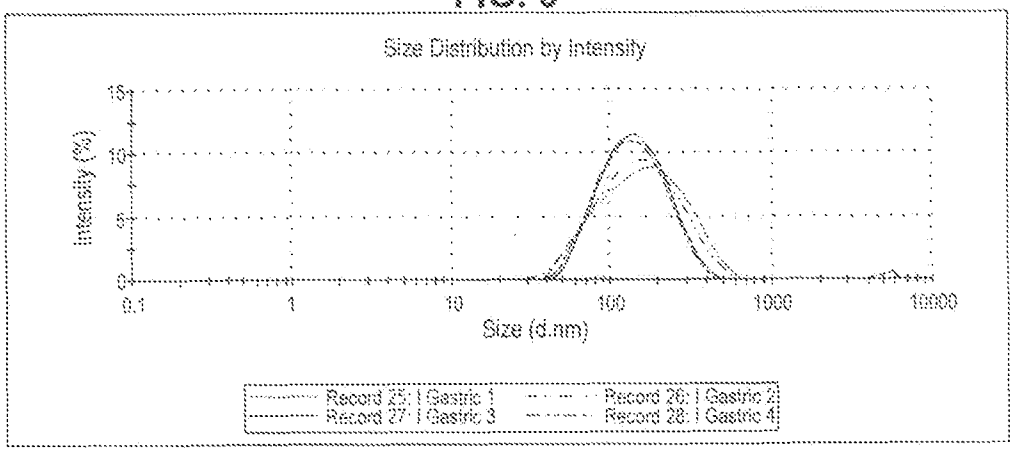

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 25: I Gastric 1
Record 26: I Gastric 2
Record 27: I Gastric 3
Record 28: I Gastric 4

FIG. 10

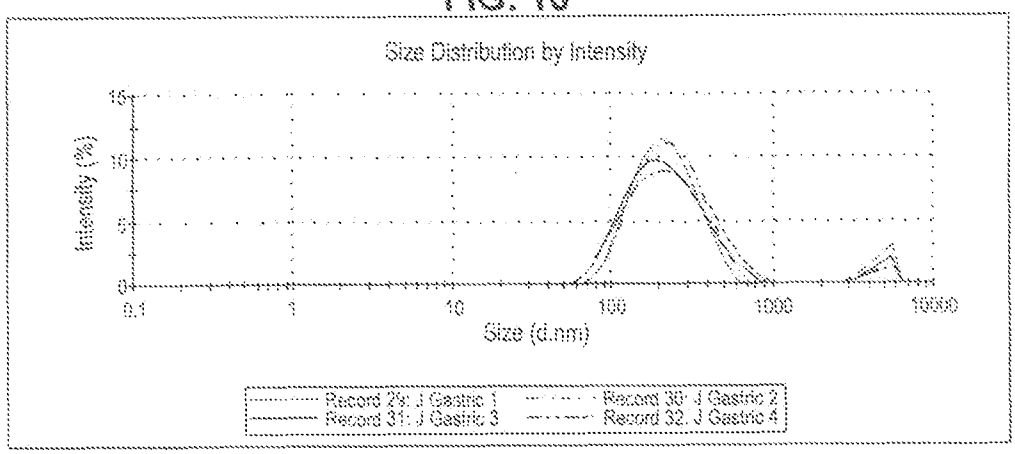

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 29: J Gastric 1
Record 30: J Gastric 2
Record 31: J Gastric 3
Record 32: J Gastric 4

FIG. 11

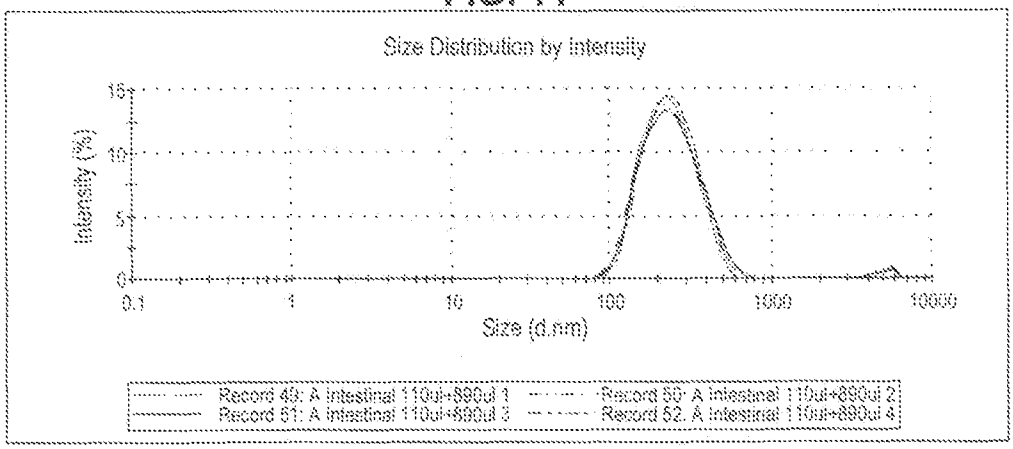

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 49: A intestinal 110ul+890ul 1
Record 50: A intestinal 110ul+890ul 2
Record 51: A intestinal 110ul+890ul 3
Record 52: A intestinal 110ul+890ul 4

FIG. 12

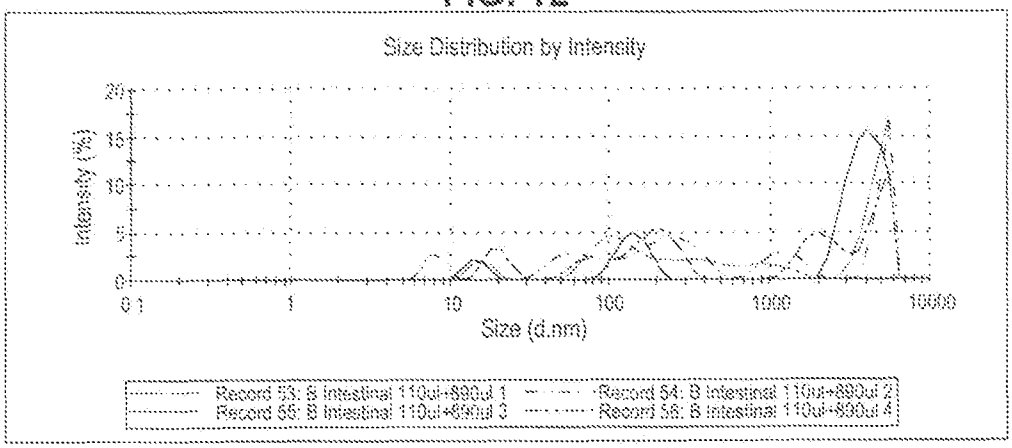

Size Distribution by Intensity
Intensity (%)
20
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 53: B intestinal 110ul+890ul 1
Record 54: B intestinal 110ul+890ul 2
Record 55: B intestinal 110ul+890ul 3
Record 56: B intestinal 110ul+890ul 4

FIG. 13

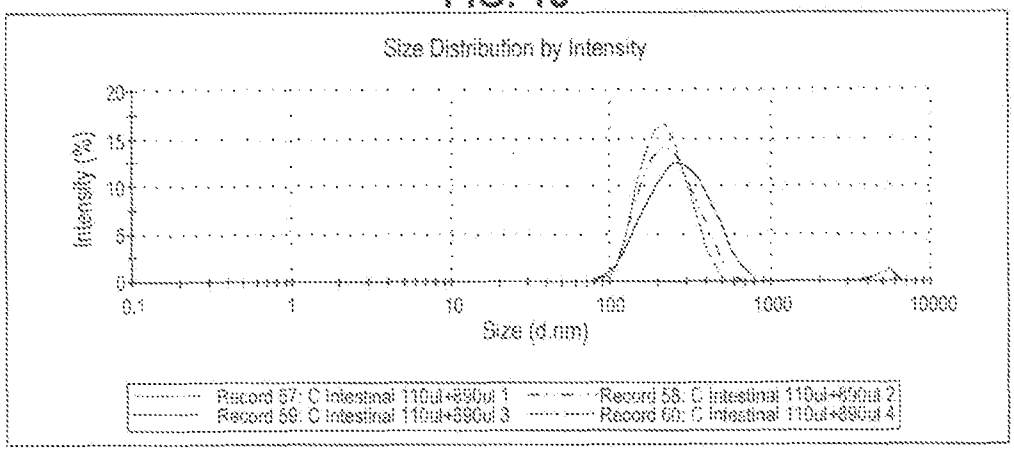

Size Distribution by Intensity
Intensity (%)
20
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 57: C Intestinal 110ul+890ul 1
Record 58: C Intestinal 110ul+890ul 2
Record 59: C Intestinal 110ul+890ul 3
Record 60: C Intestinal 110ul+890ul 4

FIG. 14

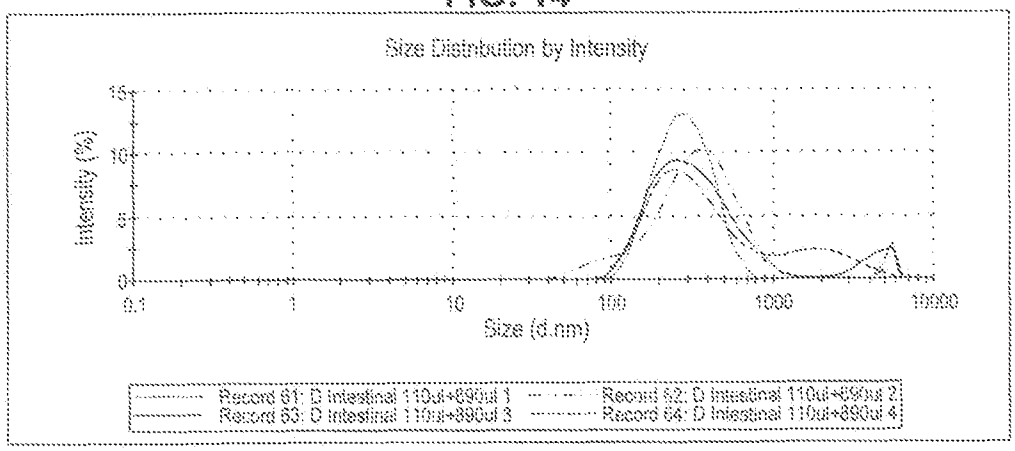

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 61: D Intestinal 110ul+890ul 1
Record 62: D Intestinal 110ul+890ul 2
Record 63: D Intestinal 110ul+890ul 3
Record 64: D Intestinal 110ul+890ul 4

FIG. 15

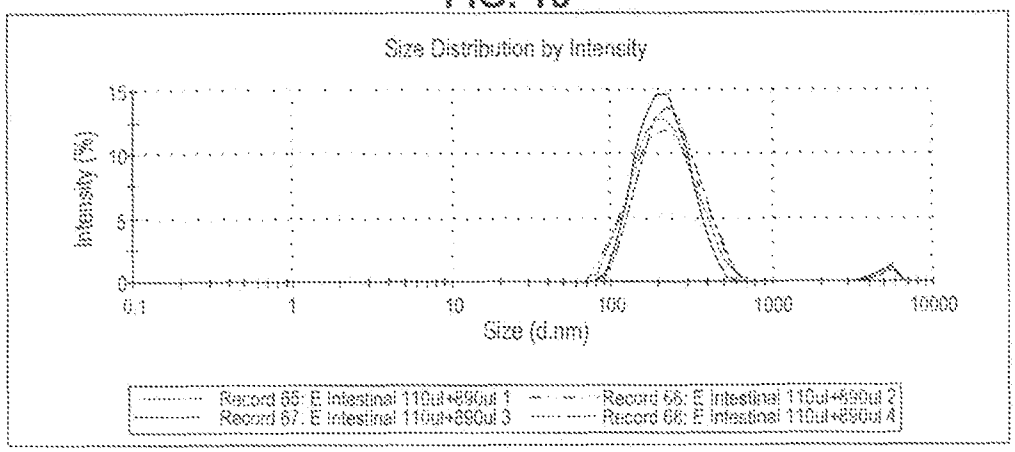

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 65: E Intestinal 110ul+890ul 1
Record 67: E Intestinal 110ul+890ul 3
Record 66: E Intestinal 110ul+890ul 4

FIG. 16

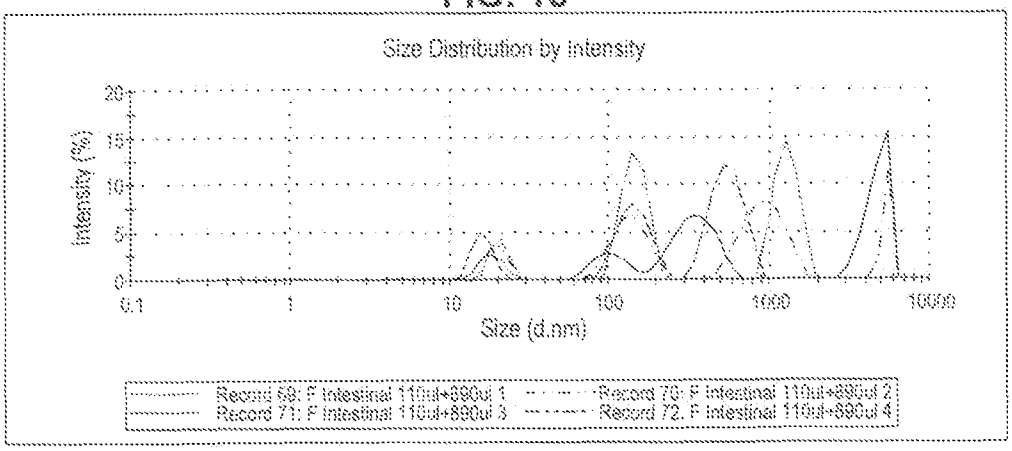

Size Distribution by Intensity
Intensity (%)
20
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 68: F Intestinal 110ul+890ul 1
Record 71: F Intestinal 110ul+890ul 3
Record 72: F Intestinal 110ul+890ul 4

FIG. 17

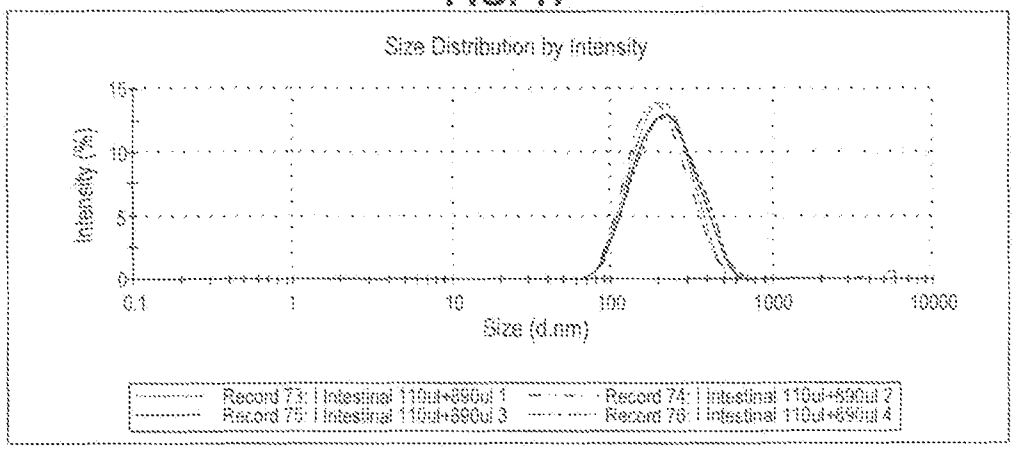

Size Distribution by Intensity
Intensity (%)
15
10
5
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 73: Intestinal 110ul+890ul 1
Record 74: Intestinal 110ul+890ul 2
Record 75: Intestinal 110ul+890ul 3
Record 76: Intestinal 110ul+890ul 4

FIG. 18

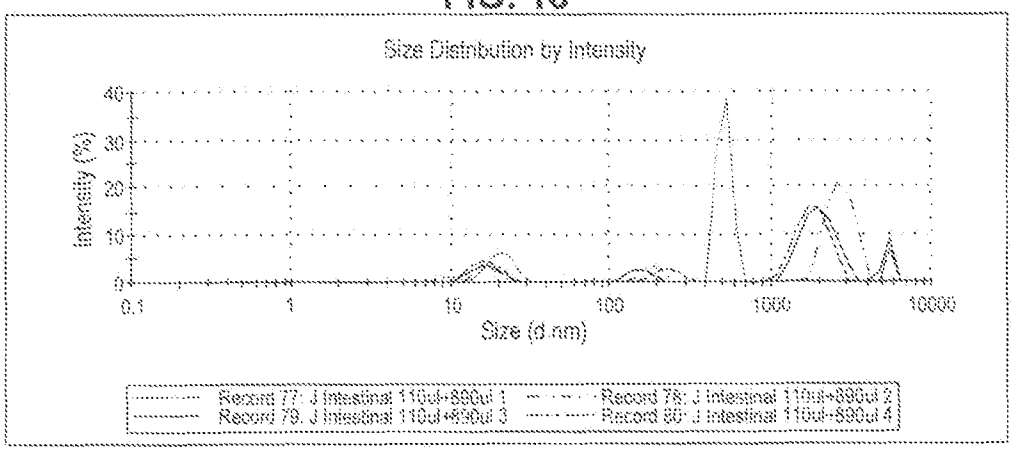

Size Distribution by Intensity
Intensity (%)
40
30
20
10
0
0.1
1
10
100
1000
10000
Size (d.nm)
Record 77: J Intestinal 110ul+890ul 1
Record 78: J Intestinal 110ul+890ul 2
Record 79: J Intestinal 110ul+890ul 3
Record 80: J Intestinal 110ul+890ul 4

FIG. 19

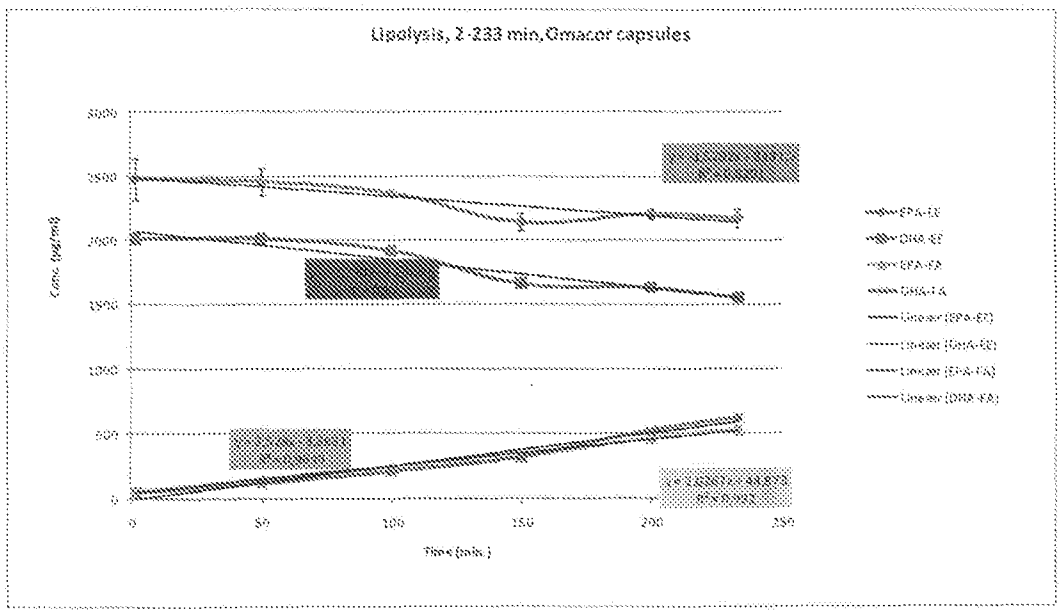

Lipolysis, 2-233 min, Omacor capsules
Time (min.)

FIG. 20

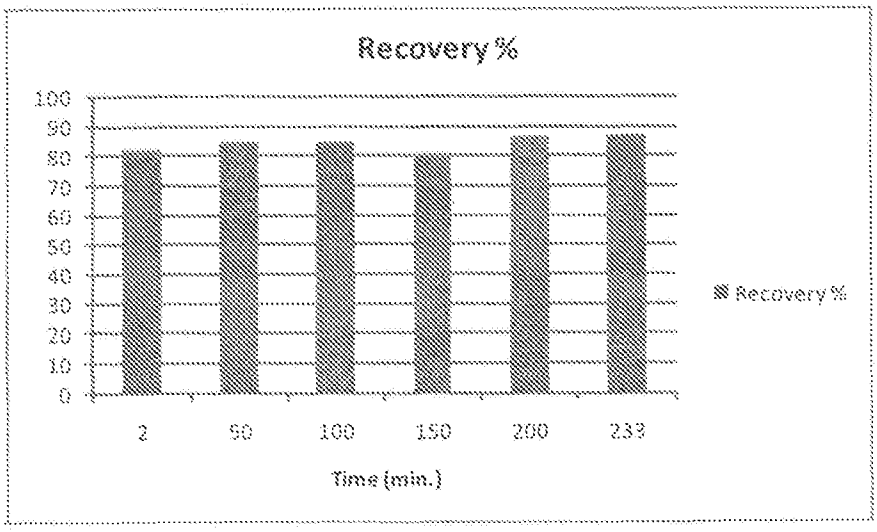

Recovery %
100
90
80
70
60
50
40
30
20
10
0
2
50
100
150
200
233
Time (min.)
Recovery %

FIG. 21

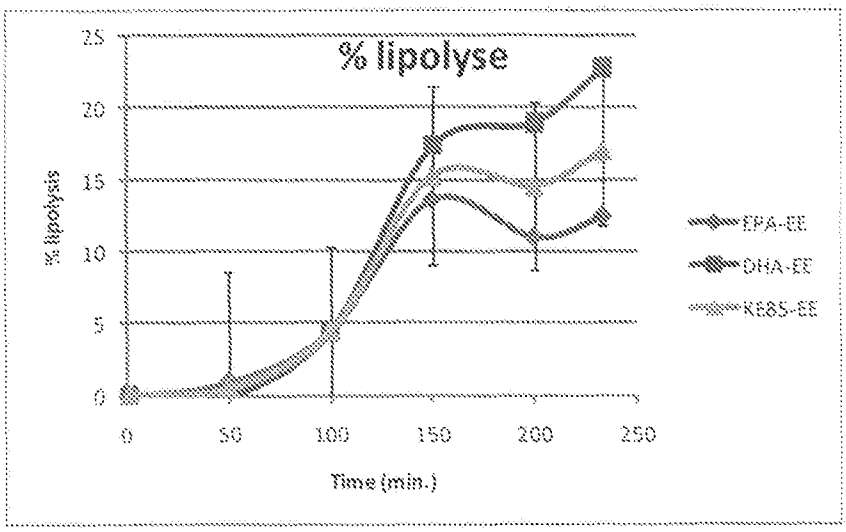

% lipolyse
% lipolysis
25
20
15
10
5
0
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
KE85-EE

FIG. 22

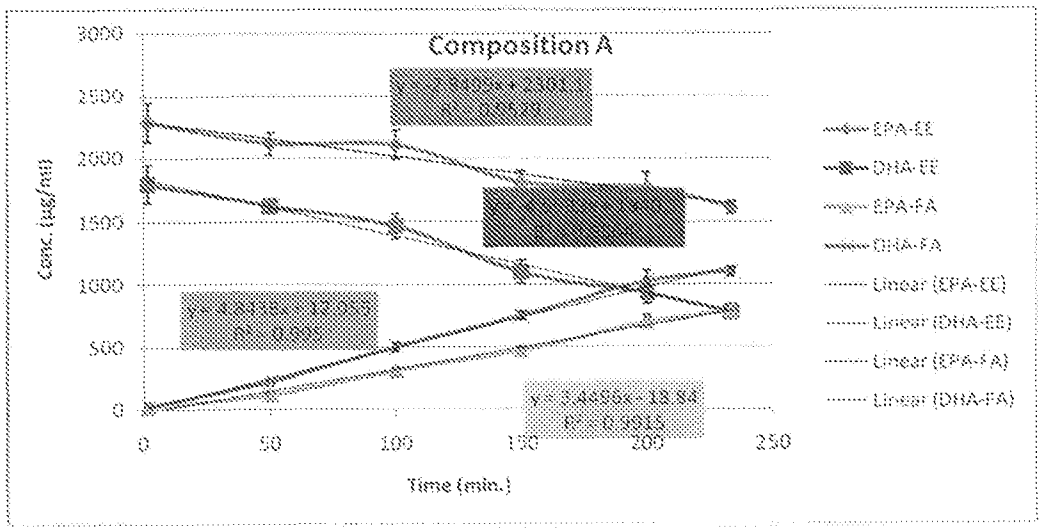

Composition A
Conc. (µg/ml)
3000
2500
2000
1500
1000
500
0
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
EPA-FA
DHA-FA
Linear (EPA-EE)
Linear (DHA-EE)
Linear (EPA-FA)
Linear (DHA-FA)

FIG. 23

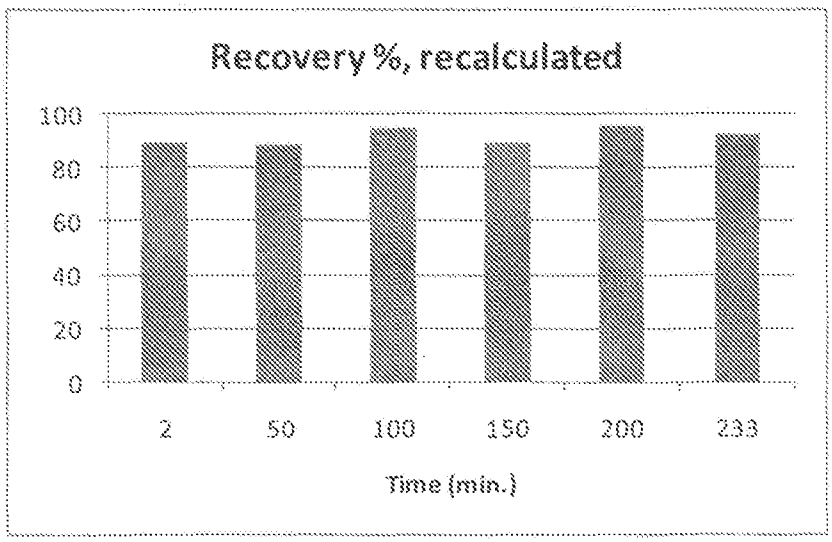

Recovery %, recalculated
100
80
60
40
20
0
2
50
100
150
200
233
Time (min.)

FIG. 24

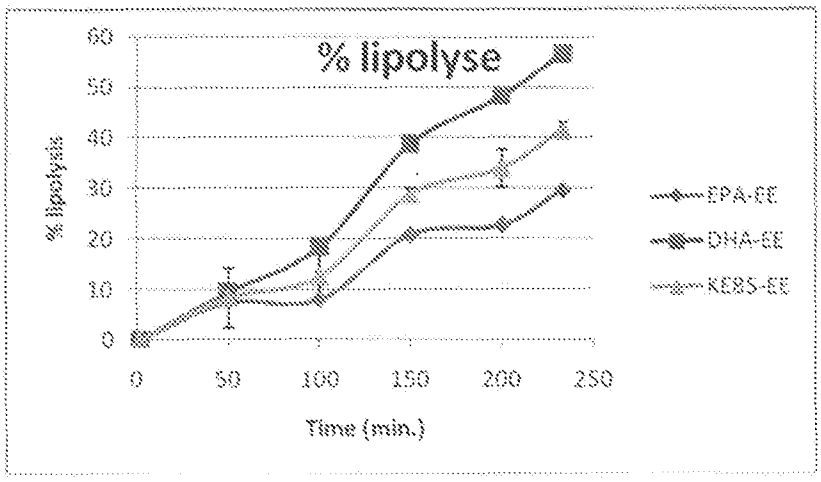

% lipolyse
60
50
40
30
20
10
0
% lipolysis
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
KERS-EE

FIG. 25

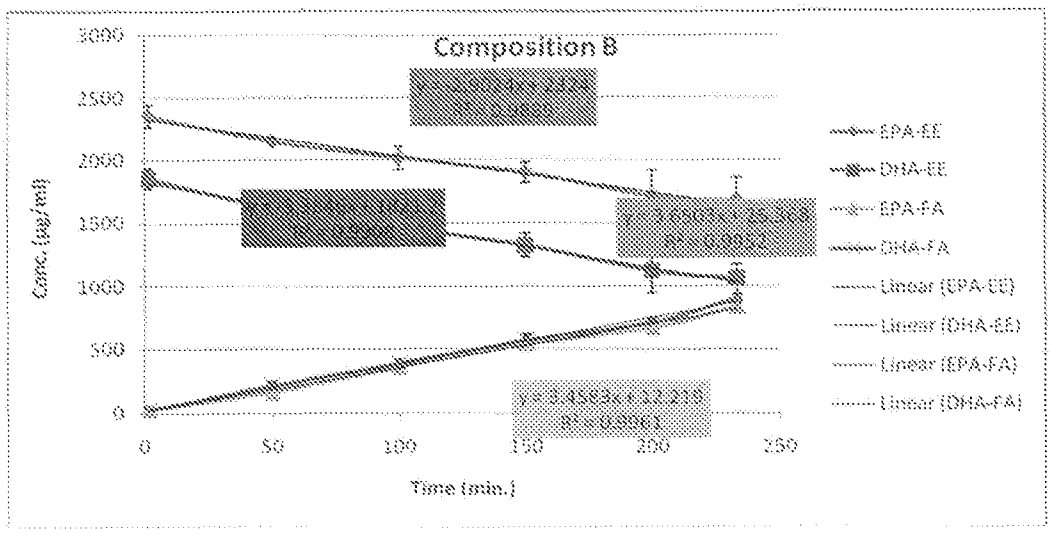

Composition B
Conc. (ug/ml)
Time (min.)
EPA-EE
DHA-EE
EPA-FA
DHA-FA
Linear (EPA-EE)
Linear (DHA-EE)
Linear (EPA-FA)
Linear (DHA-FA)

FIG. 26

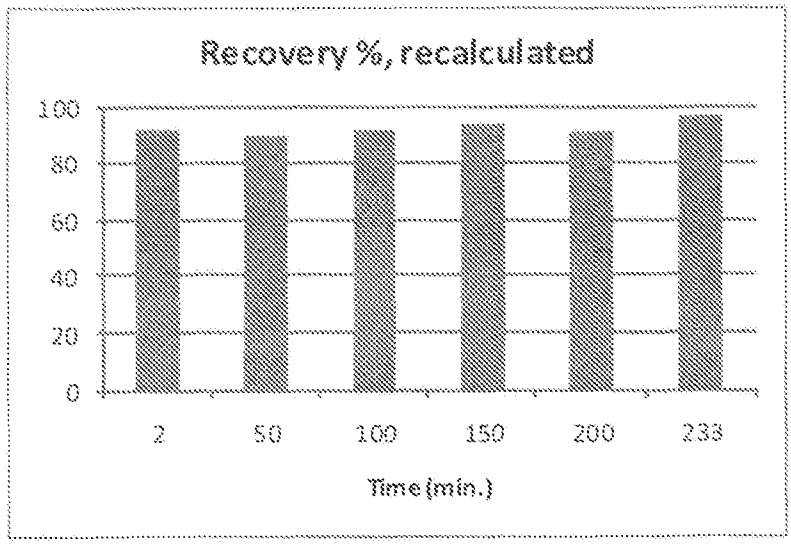

Recovery %, recalculated
Time (min.)

FIG. 27

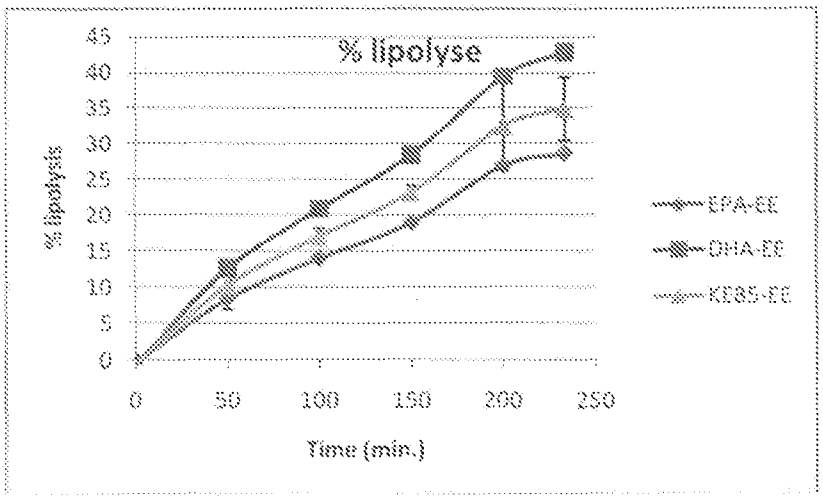

% lipolyse
% lipolysis
45
40
35
30
25
20
15
10
5
0
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
KE85-EE

FIG. 28

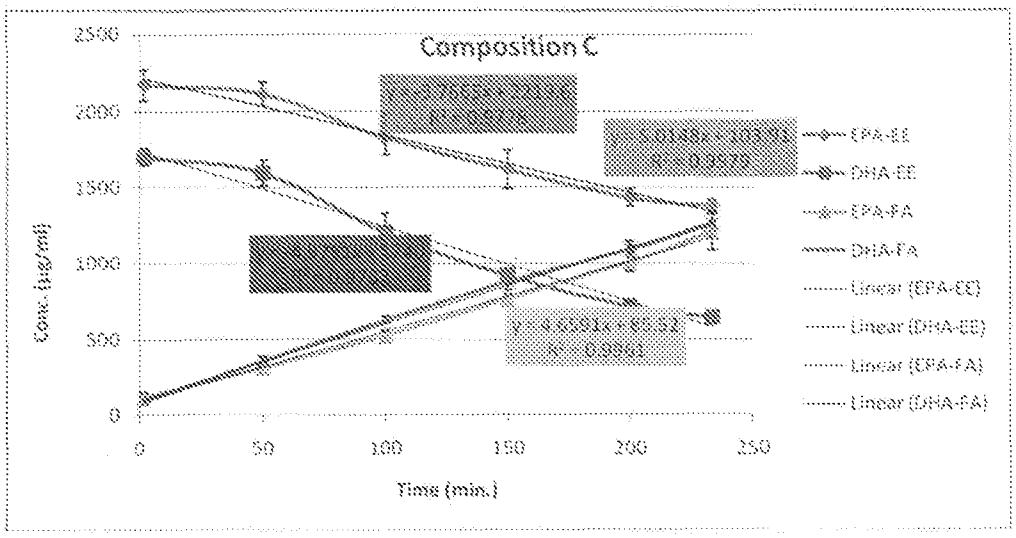

Composition C
Conc. (µg/ml)
2500
2000
1500
1000
500
0
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
EPA-FA
DHA-FA
Linear (EPA-EE)
Linear (DHA-EE)
Linear (EPA-FA)
Linear (DHA-FA)

FIG. 29

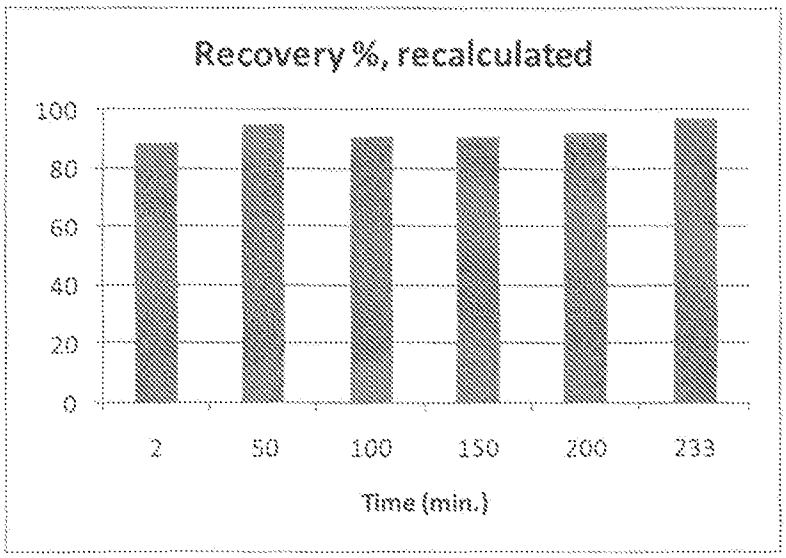

Recovery %, recalculated
100
80
60
40
20
0
2
50
100
150
200
233
Time (min.)

FIG. 30

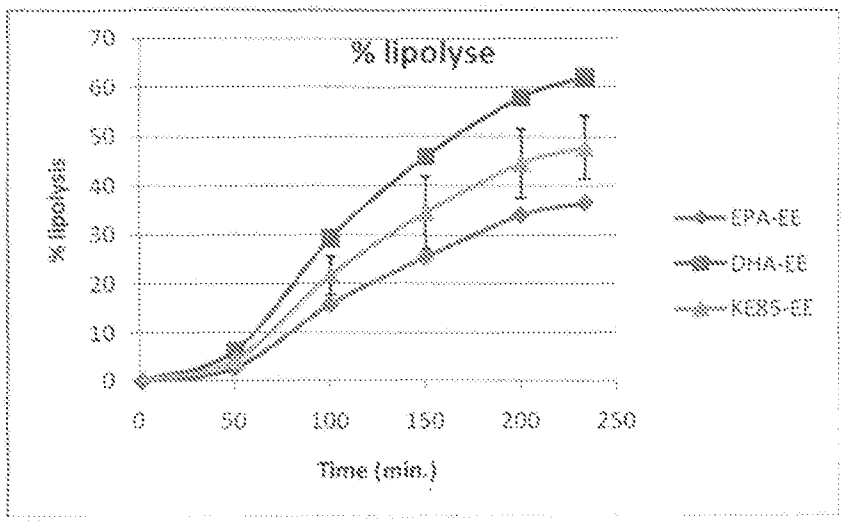

% lipolyse
70
60
50
40
30
20
10
0
% lipolysis
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
KEBS-EE

FIG. 31

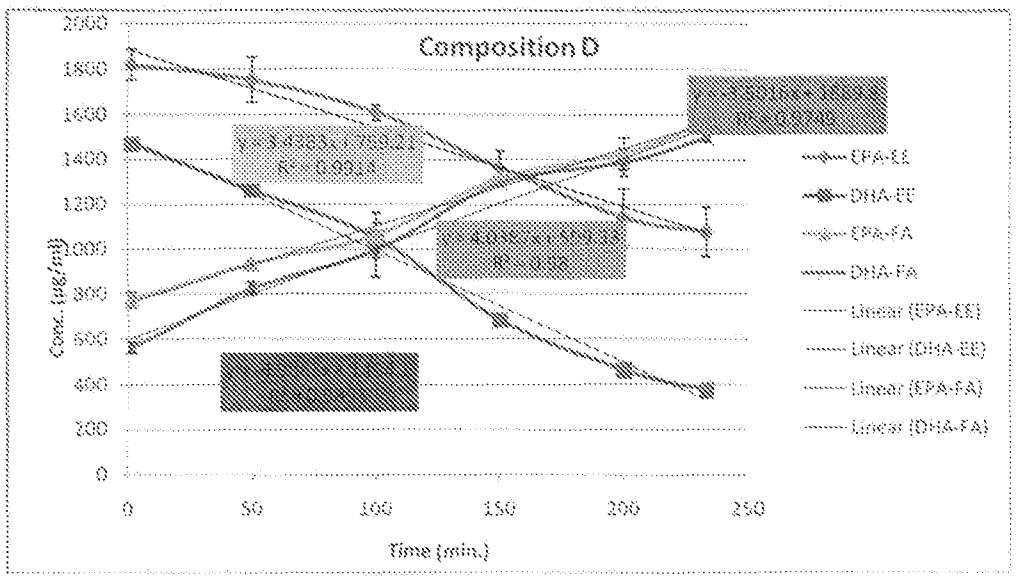

Composition D
2000
1800
1600
1400
1200
1000
800
600
400
200
0
Conc. (µg/ml)
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
EPA-FA
DHA-FA
Linear (EPA-EE)
Linear (DHA-EE)
Linear (EPA-FA)
Linear (DHA-FA)

FIG. 32

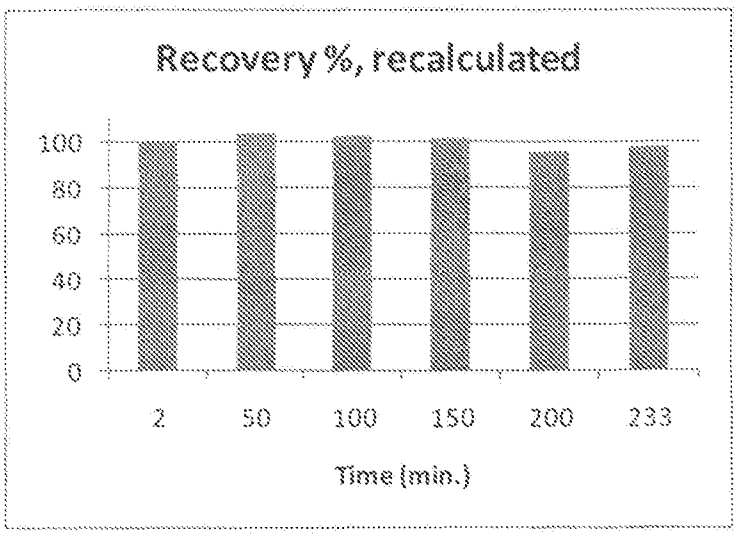

Recovery %, recalculated
100
80
60
40
20
0
2
50
100
150
200
233
Time (min.)

FIG. 33

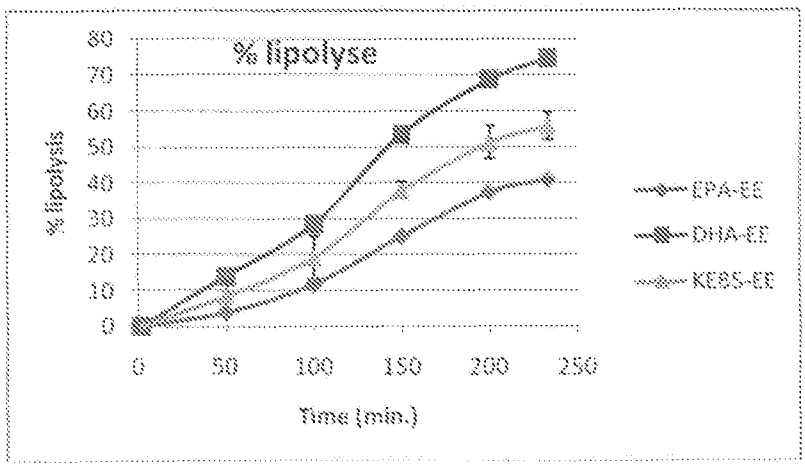

% lipolyse
% lipolysis
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
KE85-EE

FIG. 34

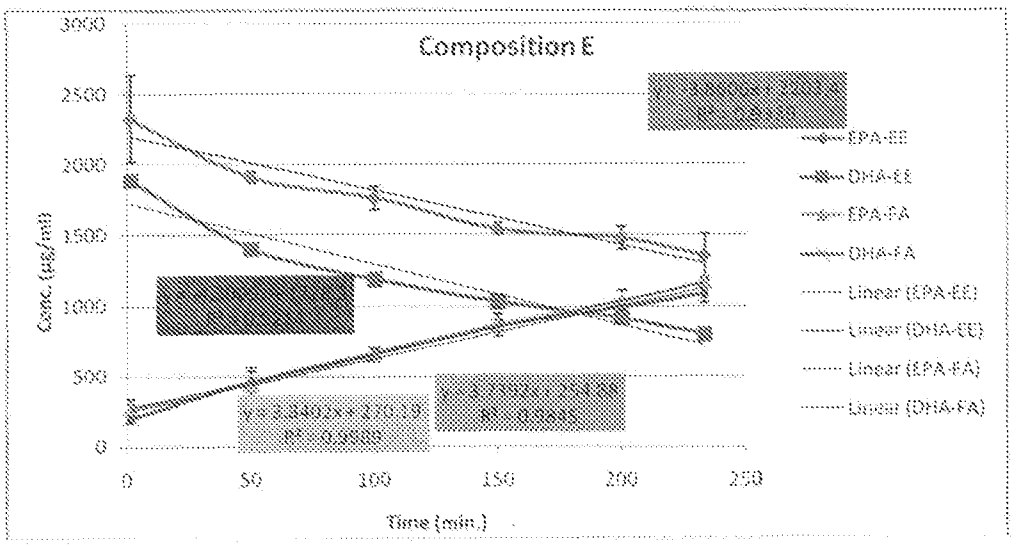

Composition E
Conc. (µg/ml)
3000
2500
2000
1500
1000
500
0
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
EPA-FA
DHA-FA
Linear (EPA-EE)
Linear (DHA-EE)
Linear (EPA-FA)
Linear (DHA-FA)

FIG. 35

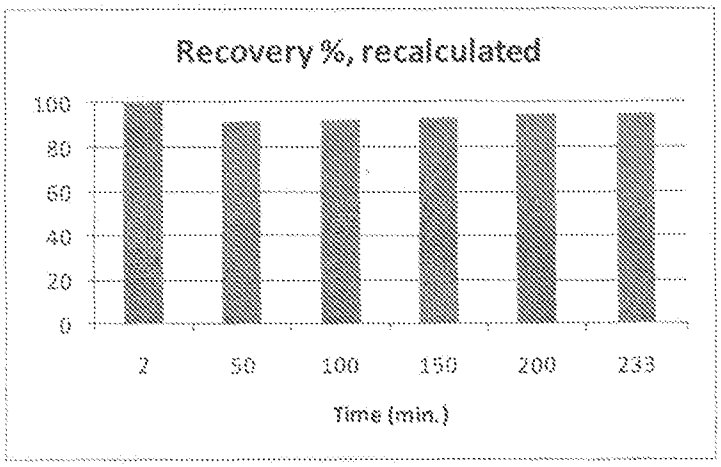

Recovery %, recalculated
100
80
60
40
20
0
2
50
100
150
200
233
Time (min.)

FIG. 36

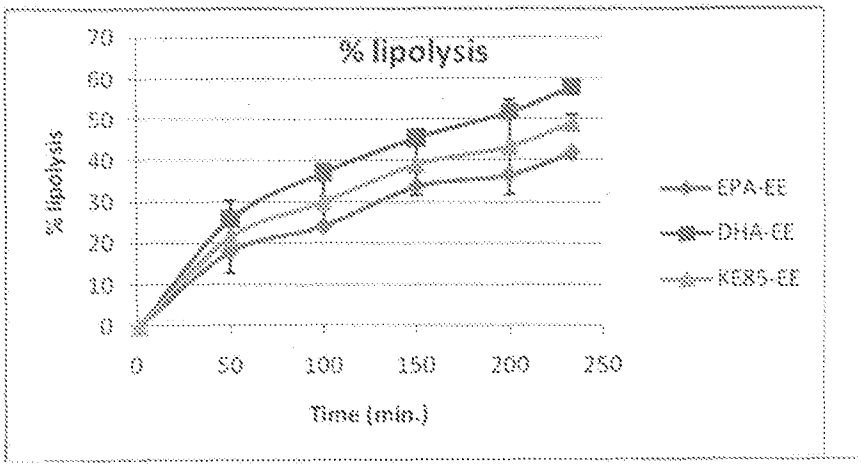
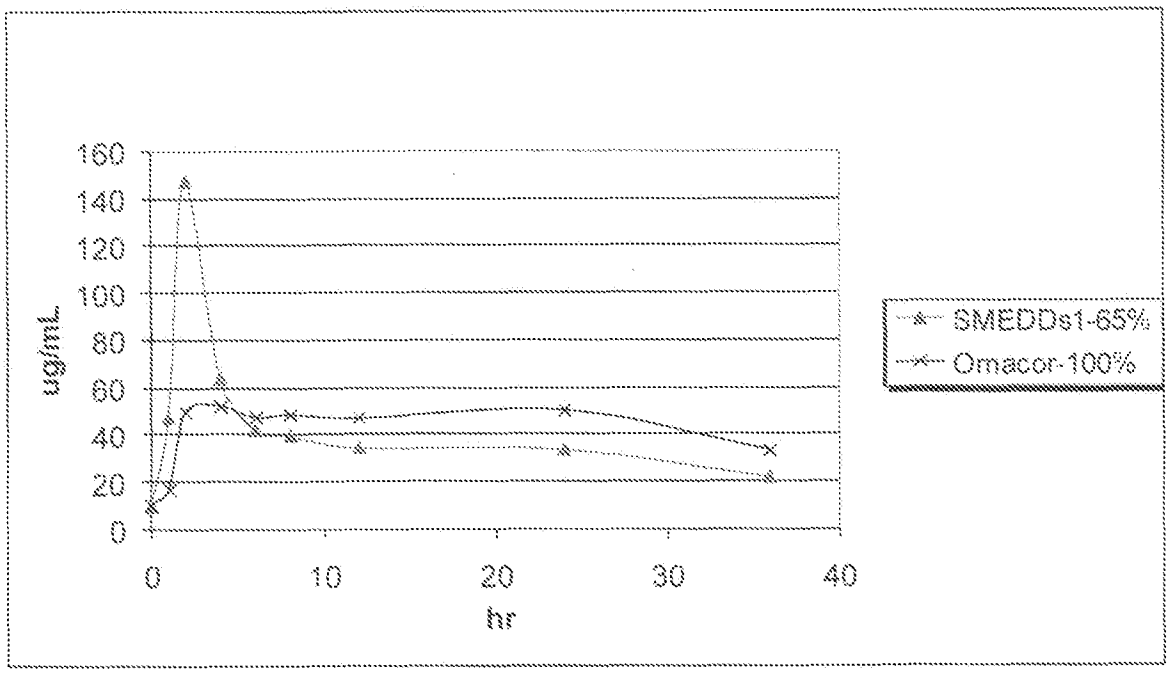

% lipolysis
70
60
50
40
30
20
10
0
% lipolysis
0
50
100
150
200
250
Time (min.)
EPA-EE
DHA-EE
KEBS-EE

FIG. 37


160
140
120
100
80
60
40
20
0
ug/mL
0
10
20
30
40
hr
SMEDDs1-65%
Omacor-100%

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/000788

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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)

IPC:A61K

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

SE, DK, FI, NO classes as above

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

EPO-Internal, PAJ, WPI data, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE, IBM-TDB

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document. with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004056370 A1 (PRONOVA BIOCARE AS ET AL), 8 July 2004 (2004-07-08); abstract; page 11, line 30 - page 12, line 4; claims 1, 9, 11	1-196
X	WO 9956727 A1 (ELAN CORP PLC ET AL), 11 November 1999 (1999-11-11); page 11, line 8 - page 11, line 21; claims 1, 7; Example 7, table 11	1-196
X	WO 9929316 A1 (SEVERSON MARY L ET AL), 17 June 1999 (1999-06-17); claims 1, 7-8; Example 11, table 1	1-196
A	US 20090011012 A1 (BAUM SETH J), 8 January 2009 (2009-01-08); abstract; claims 17-18	1-196
A	US 5502077 A1 (BREIVIK HARALD ET AL), 26 March 1996 (1996-03-26); claims	1-196
A	GB 2033745 A (WELLCOME FOUND), 29 May 1980 (1980-05-29); claims 1-4, 10-17	1-196

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10-08-2010	10-08-2010
Name and mailing address of the ISA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Ingrid Eklund Telephone No. + 46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/000788

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1157692 A1 (QUATEX NV - (B1) PRO APARTS INVESTIMENTOS E CON [PT]), 28 November 2001 (2001-11-28); claims 1-9 --	1-196
A	WO 9929335 A1 (CHONG KUN DANG CORP ET AL), 17 June 1999 (1999-06-17); abstract; section[0041], table 3, formulations aA-D --	1-196
A	US 20090030077 A1 (ALMARSSON ORN ET AL), 29 January 2009 (2009-01-29); Example 3B --	1-196
X	US 20070141138 A1 (FEUERSTEIN SETH D ET AL), 21 June 2007 (2007-06-21); Table 1 -- ----------	1

Continuation of: second sheet

International Patent Classification (IPC)

A61K 9/66 (2006.01)
A61K 31/202 (2006.01)
A61K 31/557 (2006.01)
A61K 9/08 (2006.01)
A61K 9/107 (2006.01)
A61K 9/20 (2006.01)

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Use the application number as username. The password is **GRDVHCZRPV**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2010/000788

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 105-142
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 105-142 relate to a method for treatment of the human or animal body by

.../...

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of: Box No. II

surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.

International application No.
PCT/IB2010/000788

Continuation of: Box No. III

Invention 1: Claims 1-142, 173 partly, 174, 176 partly, 177, 179-188 partly, 189-191, 192-193 partly, 194-195, 196

Invention 1 is directed to a pharmaceutical composition comprising a fatty acid oil mixture comprising at least 75% EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid.

Invention 2: Claims 143-172, 173 partly, 175, 176 partly, 178, 179-188 partly, 192-193 partly

Invention 2 is directed to a food supplement or nutritional supplement composition comprising a fatty acid oil mixture comprising from about 25 % to about 75 % EPA and DHA by weight of the fatty acid oil mixture, wherein the EPA and DHA are in a form chosen from ethyl ester and triglyceride; and at least one free fatty acid.

WO	2004056370	A1	08/07/2004	AU	2003288606	A1	14/07/2004
WO	9956727	A2	11/11/1999	AU	3843999	A	23/11/1999
				CA	2331640	A1	11/11/1999
				EP	1075252	A2	14/02/2001
				JP	2002513750	T	14/05/2002
WO	9929316	A1	17/06/1999	AU	743098	B2	17/01/2002
				AU	1817499	A	28/06/1999
				CA	2313024	A1	17/06/1999
				EP	1039893	A1	04/10/2000
				JP	2001525363	T	11/12/2001
				NO	20002991	A	09/08/2000
				NO	328722	B1	03/05/2010
				US	6284268	B1	04/09/2001
US	20090011012	A1	08/01/2009	CA	2692394	A1	15/01/2009
				WO	2009009040	A3	26/03/2009
US	5502077	A	26/03/1996	NONE			
GB	2033745	A	29/05/1980	NONE			
EP	1157692	A1	28/11/2001	AT	305810	T	15/10/2005
				DE	60022987	D1	10/11/2005
				ES	2246769	T3	01/03/2006
				PL	347655	A1	03/12/2001
WO	9929335	A1	17/06/1999	AU	1509799	A	28/06/1999
				KR	100300251	B1	15/06/2001
US	20090030077	A1	29/01/2009	NONE			
US	20070141138	A1	21/06/2007	US	20100130611	A1	27/05/2010
				US	20100112047	A1	06/05/2010
				US	20080268042	A1	30/10/2008
				US	7652068	B2	26/01/2010