TITLE

STABLE PHARMACEUTICAL COMPOSITION AND METHODS OF USING SAME

PRIORITY CLAIM

[0001] This application claims priority from U.S. provisional patent application 61/173,763, filed April 29, 2009, the entirety of which is hereby incorporated by reference herein.

BACKGROUND

[0002] Mixed omega-3 fatty acid esters are typically encapsulated in type 2a gelatin capsules containing gelatin (~43.4%), glycerol (~20%) and water (~36.6%) and do not experience stability problems throughout their shelf life. While chemically modified gelatins such as succinated/succinylated gelatin have been used to encapsulate reactive fill ingredients, such gelatin is not approved for use in the U.S. and other markets.

SUMMARY

[0003] We have unexpectedly found that high purity eicosapentaenoic acid (EPA) is more susceptible to oxidative degradation than mixed omega-3-acid ethyl esters. In various examples, the disclosure provides pharmaceutical compositions comprising a fatty acid or a derivative thereof in a capsule shell that resists, hinders, attenuates, or prevents oxidation of the fatty acid or fatty acid derivative, for example to a greater extent than is provided by a standard type IIa capsule shell. In a related example, the fatty acid comprises eicosapentaenoic acid (EPA) or a derivative of EPA, for example ethyl eicosapentaenoate (ethyl-EPA or E-EPA). In another example, the fatty acid comprises ultra-pure EPA.

[0003a] In one aspect, the present disclosure refers to a pharmaceutical composition comprising 95% to 99.9% ethyl-EPA enclosed in a capsule shell, wherein (a) the pharmaceutical composition has a baseline peroxide from 0 meq/kg to 5 meq/kg and upon storage of the pharmaceutical composition at 25°C and 60% RH for a period of 6 months, the pharmaceutical composition has a second peroxide value from 0 meq/kg to 8 meq/kg, (b) the capsule shell is free of succinated gelatin and comprises a film-forming material, a hygroscopic plasticizer selected from glycerin, sorbitol and alkylene glycols, and a non-hygroscopic plasticizer selected from maltitol, lactitol, xylitol, hydrogenated starch hydrolysate and glucose syrup, wherein the hygroscopic plasticizer and the non-hygroscopic plasticizer are present in a weight ratio of 2:1 to 6:1, and (c) if the capsule shell comprises

glycerin and the film-forming material comprises gelatin, the capsule shell has a gelatin:glycerin weight ratio of 5:1 to 8:1.

[0003b] In another aspect, the present disclosure refers to a pharmaceutical composition comprising 95% to 99.9% ethyl-EPA enclosed in a capsule shell comprising a film-forming material free of chemically modified gelatin, a hygroscopic plasticizer selected from glycerin, sorbitol and alkylene glycols, and a non-hygroscopic plasticizer selected from maltitol, lactitol, xylitol, hydrogenated starch hydrolysate and glucose syrup, wherein the capsule shell has a weight ratio of hygroscopic plasticizer to non-hygroscopic plasticizer of 2:1 to 6:1, wherein if the capsule shell comprises glycerin and the film-forming material comprises gelatin, the capsule shell has a gelatin:glycerin weight ratio of 5:1 to 10:1, and wherein the pharmaceutical composition has a baseline peroxide value from 0 meq/kg to 5 meq/kg and upon storage of the pharmaceutical composition at 30°C and 65% RH for a period of 6 months, the pharmaceutical composition has a second peroxide value from 0 meq/kg to 5 meq/kg.

[0003c] In yet another aspect, the present disclosure refers to a pharmaceutical composition comprising 95% to 99.9% ethyl-EPA encapsulated in a capsule shell comprising non-chemically modified gelatin, a hygroscopic plasticizer selected from glycerin, sorbitol and alkylene glycols, and a non-hygroscopic plasticizer selected from maltitol, lactitol, xylitol, hydrogenated starch hydrolysate and glucose syrup, wherein the capsule shell has a weight ratio of gelatin to total plasticizer of 1.75:1 to 5:1 and a weight ratio of hygroscopic plasticizer to non-hygroscopic plasticizer of 3:1 to 5:1, wherein the pharmaceutical composition has a baseline peroxide value of 0 meq/kg to 5 meq/kg and upon storage of the pharmaceutical composition at 25°C and 60% RH for a period of 6 months, the pharmaceutical composition has a second peroxide value of 0 meq/kg to 8 meq/kg, and wherein if the hygroscopic plasticizer comprises glycerin, the capsule shell has a gelatin:glycerin weight ratio of 5:1 to 10:1.

[0003d] In yet another aspect, the present disclosure refers to use of a pharmaceutical composition disclosed herein in the manufacture of a medicament for treating or preventing a cardiovascular-related disease in a subject in need thereof, wherein 2 g per day to 4 g per day of said composition is to be administered to the subject.

[0004] In one example, the disclosure provides a pharmaceutical composition comprising ultra-pure EPA encapsulated in a capsule shell, where the ultra-pure EPA has a baseline peroxide value not greater than about 5 Meq/kg and upon storage of the composition at 23 °C

and 50% RH for a period of time, that ultra-pure EPA has a second peroxide value not greater than about 20 Meq/kg.

[0005] In other examples, the disclosure provides a pharmaceutical composition comprising EPA (e.g. E-EPA or ultra pure E-EPA) encapsulated in a capsule shell comprising a film forming material and a hygroscopic plasticizer, wherein the weight ratio of film-forming material to hygroscopic plasticizer is not less than about 2.5:1. Further, the capsule shell can optionally comprise a non-hygroscopic plasticizer. In one example, the

capsule contains no chemically modified gelatin, for example succinated or succinylated gelatin.

[0006] In still other examples, the present disclosure provides methods of treating or preventing a cardiovascular-related disease using compositions as described herein.

[0007] These and other embodiments of the present invention will be disclosed in further detail herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0008] Fig. 1 shows dissolution profile of an inventive capsule composition containing ~500 mg E-EPA versus a composition comprising EPA in a succinated gelatin capsule.

[0009] Fig. 2 shows bioavailability of 300 mg of EPA in succinated gelatin capsules.

[0010] Fig. 3 shows bioavailability of an inventive AMR101 capsule composition containing ~500 mg E-EPA.

DETAILED DESCRIPTION

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

[0012] The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." In this manner, slight variations from a stated value can be used to achieve substantially the same results as the stated value. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a recited numeric value into any other recited numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.