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.

[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. In one aspect, the present disclosure refers to a use of a pharmaceutical composition in the manufacture of a medicament comprising at least about 95%, by weight of all fatty acids present, ethyl eicosapentaenoate in one or more capsules comprising a capsule wall composed of a film-forming material that is free of succinated gelatin for lowering triglycerides without increasing LDL-C in a subject having fasting baseline triglycerides of 500 mg/dl to about 1500 mg/dl, wherein the pharmaceutical composition is to be administered in an amount and for a period effective to reduce triglycerides by at least 25% without increasing LDL-C in the subject compared to a second subject having fasting baseline triglycerides of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition. In another aspect, the present disclosure refers to a use of a pharmaceutical composition in the manufacture of a medicament comprising about 2,500 mg to 5,000 mg ethyl eicosapentaenoate present in one or more capsules for treating a subject with fasting triglycerides of at least 500 mg/dl, wherein the pharmaceutical composition is to be administered orally to the subject daily for a period of 12 weeks and effective to lower triglycerides in the subject by at least 25% without increasing LDL-C by more than 5%. In yet another aspect, the present disclosure refers to a use of a pharmaceutical composition in the manufacture of a medicament comprising 2,500 mg to 5,000 mg of fatty acids, at least about 95% by weight of which are ethyl eicosapentaenoate for treating mixed dyslipidemia in a subject on statin therapy, wherein upon 12 weeks of said administration the subject exhibits a reduction in triglycerides of at least 15% and a reduction in LDL-C of at least 5% compared to placebo control. In another aspect, the present disclosure refers to a use of a pharmaceutical composition in the manufacture of a medicament comprising 2,000 mg to about 5,000 mg of ethyl eicosapentaenoate, present in one or more capsules, for reducing triglycerides in a subject with fasting baseline triglycerides of at least 500 mg/dl by at least about 20% compared to a second subject with fasting baseline triglycerides of at least about 500 mg/dl who has not received the pharmaceutical composition, wherein the pharmaceutical composition is to be administered orally daily for a period of 12 weeks.

[0007] These and other examples of the present disclosure 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.

CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition in the manufacture of a medicament comprising at least about 95%, by weight of all fatty acids present, ethyl eicosapentaenoate in one or more capsules comprising a capsule wall composed of a film-forming material that is free of succinated gelatin for lowering triglycerides without increasing LDL-C in a subject having fasting baseline triglycerides of 500 mg/dl to about 1500 mg/dl, wherein the pharmaceutical composition is to be administered in an amount and for a period effective to reduce triglycerides by at least 25% without increasing LDL-C in the subject compared to a second subject having fasting baseline triglycerides of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition.

2. The use according to claim 1, wherein the film-forming material comprises gelatin, carrageenan, alkylated or hydroxyalkylated cellulose ethers, starch, alpha-starch, hydroxyalkyl starch, sodium alginate, sodium salt of a gelatin copolymer and acrylic acid, hydroxypropyl methyl cellulose, hydroxyethyl cellulose or polyvinyl alcohol.

3. The use according to claim 1, wherein the film-forming material comprises at least one plasticizer.

4. The use according to claim 1, wherein the at least one plasticizer comprises a hygroscopic plasticizer.

5. The use according to claim 4, wherein the hygroscopic plasticizer comprises glycerol.

6. The use according to claim 1, wherein the film-forming material comprises gelatin.

7. The use according to claim 1, wherein the composition is to be administered to the subject for a period effective to reduce triglycerides by at least 30% without increasing LDL-C compared to the second subject.

8. The use according to claim 7, wherein the composition is to be administered to

the subject for a period effective to reduce triglycerides by at least about 35% without increasing LDL-C compared to the second subject.

9. The use according to claim 1, wherein said period is at least about 12 weeks.

10. The use according to claim 1, wherein the composition is to be administered to the subject to affect a reduction in apolipoprotein B compared to the second subject.

11. The use according to claim 1, wherein the composition is to be administered to the subject to affect at least a 5% reduction in apolipoprotein B compared to the second subject.

12. Use of a pharmaceutical composition in the manufacture of a medicament comprising about 2,500 mg to 5,000 mg ethyl eicosapentaenoate present in one or more capsules for treating a subject with fasting triglycerides of at least 500 mg/dl, wherein the pharmaceutical composition is to be administered orally to the subject daily for a period of 12 weeks and effective to lower triglycerides in the subject by at least 25% without increasing LDL-C by more than 5%.

13. The use according to claim 12, wherein the subject has a fasting baseline LDL-C from about 50 mg/dl to about 300 mg/dl.

14. The use according to claim 12, wherein the subject has one or more of: a baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a baseline fasting HDL-C of about 10 mg/dl to about 80 mg/dl.

15. The use according to claim 12, wherein the pharmaceutical composition is to be administered to the subject daily for the period of 12 weeks to affect a reduction in triglycerides of at least about 30% without increasing LDL-C in the subject.

16. The use according to claim 12, wherein the pharmaceutical composition is to be

administered to the subject daily for the period of 12 weeks to affect a reduction in apolipoprotein B in the subject.

17. The use according to claim 12, wherein the pharmaceutical composition is to be administered to the subject daily for the period of 12 weeks to affect a reduction in VLDL-C in the subject.

18. Use of a pharmaceutical composition in the manufacture of a medicament comprising 2,500 mg to 5,000 mg of fatty acids, at least about 95% by weight of which are ethyl eicosapentaenoate for treating mixed dyslipidemia in a subject on statin therapy, wherein upon 12 weeks of said administration the subject exhibits a reduction in triglycerides of at least 15% and a reduction in LDL-C of at least 5% compared to placebo control.

19. The use according to claim 18, wherein upon 12 weeks of said administration the subject exhibits a reduction in fasting triglycerides of at least 20% compared to placebo control.

20. The use according to claim 18, wherein upon 12 weeks of said administration the subject exhibits a reduction in fasting apolipoprotein B compared to placebo control.

21. The use according to claim 18, wherein upon 12 weeks of said administration the subject exhibits a reduction in fasting VLDL-C compared to placebo control.

22. The use according to claim 18, wherein upon 12 weeks of said administration the subject exhibits a reduction in fasting VLDL-C of at least 10% compared to placebo control.

23. The use according to claim 18, wherein the ethyl eicosapentaenoate is to be administered to the subject in capsules each comprising about 900 mg to about 1 g of ethyl eicosapentaenoate.

24. The use according to claim 18, wherein the ethyl eicosapentaenoate is to be

administered to the subject in capsules each comprising about 1 g of ethyl eicosapentaenoate.

25. Use of a pharmaceutical composition in the manufacture of a medicament comprising 2,000 mg to about 5,000 mg of ethyl eicosapentaenoate, present in one or more capsules, for reducing triglycerides in a subject with fasting baseline triglycerides of at least 500 mg/dl by at least about 20% compared to a second subject with fasting baseline triglycerides of at least about 500 mg/dl who has not received the pharmaceutical composition, wherein the pharmaceutical composition is to be administered orally daily for a period of 12 weeks.

26. The use according to claim 25, wherein the subject and the second subject have a median fasting baseline LDL-C from about 50 mg/dl to about 300 mg/dl.

27. The use according to claim 25, wherein the subject and the second subject have one or more of: a median baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a median baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a median baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a median baseline fasting HDL-C of about 10 mg/d1 to about 80 mg/dl.

28. The use according to claim 25, wherein the pharmaceutical composition is to be administered to the subject daily for the period of 12 weeks to affect a reduction in triglycerides of at least about 25% without increasing LDL-C in the subject compared to the second subject.

29. The use according to claim 25, wherein the pharmaceutical composition is to be administered to the subject daily for the period of 12 weeks to affect a reduction in triglycerides of at least about 30% without increasing LDL-C in the subject compared to the second subject.

30. The use according to claim 25, wherein the pharmaceutical composition is to be administered to the subject daily for the period of 12 weeks to affect a reduction in VLDL-C in the subject compared to the second subject.