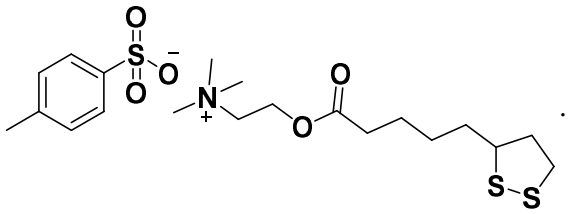
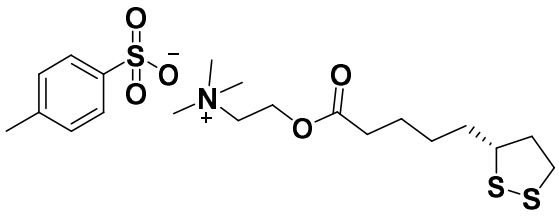
What is claimed is:

1. Lipoic acid choline ester tosylate having structure:

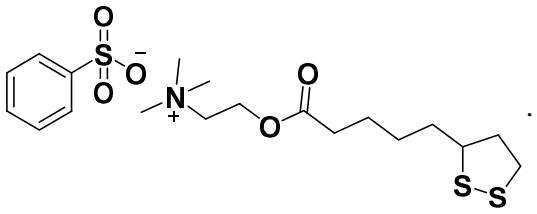


2. (R) Lipoic acid choline ester tosylate having structure:

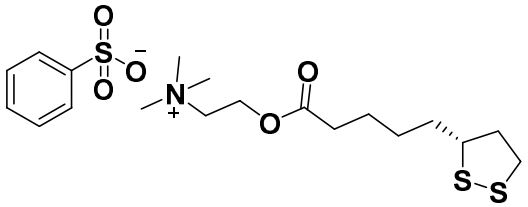


having at least 90% enantiomeric excess of the R isomer.

3. Lipoic acid choline ester besylate having structure:

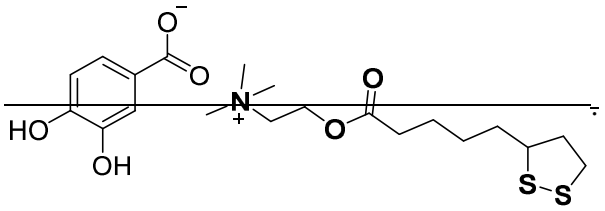


4. (R) Lipoic acid choline ester besylate having structure:

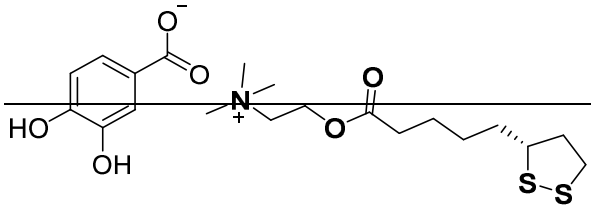


having at least 90% enantiomeric excess of the R isomer.

~~5. Lipoic acid choline ester 3,4-dihydroxybenzoate, having structure:~~



~~6. (R) Lipoic acid choline ester 3,4-dihydroxybenzoate, having structure:~~



~~having at least 90% enantiomeric excess of the R-isomer.~~

~~7.~~5. A crystal form A of lipoic acid choline ester ~~(LACE)~~ tosylate characterized by an X ray diffraction pattern having three or more peaks at 2θ values selected from 21.9, 24.9, 25.9, 26.7, 27.1, 30.4, and 32.1 ± 0.2 °2θ.

~~8.~~6. The crystal form A of lipoic acid choline ester~~LACE~~ tosylate according to claim ~~7~~5, characterized by an X ray diffraction pattern having four, five, six, or seven peaks at 2θ values selected from 11.4, 15.2, 18.4, 19.0, 19.4, 19.8, 21.9, 22.9, 24.9, 25.9, 26.7, 27.1, 29.6, 30.4, 32.1± 0.2 °2θ.

~~9. A crystal form A of LACE tosylate having a X-ray diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in FIGURE 4.~~

~~10.~~7. A crystal form B of lipoic acid choline ester ~~(LACE)~~ tosylate characterized by an X ray diffraction pattern having three or more peaks at 2θ values selected from 7.7, 20.7, 21.4, 24.3, and 25.37 ± 0.2 °2θ.

~~11.~~8. The crystal form B of lipoic acid choline ester~~LACE~~ tosylate according to claim ~~7~~10, characterized by an X ray diffraction pattern having four or five peaks at 2θ values selected from 7.7, 20.7, 21.4, 24.3, and 25.37 ± 0.2 °2θ.

~~12. A crystal form B of LACE tosylate having a X-ray diffraction pattern substantially the same as the X-ray powder diffraction pattern shown in FIGURE 8.~~

~~13.~~9. A lipoic acid choline ester~~lipoic acid choline~~ tosylate composition, comprising at least 90 weight % of the crystalline form B according to ~~any one of~~ claim~~s~~ 7 or 8~~10-12~~, based on the weight of the composition.

~~14. A method of preparing a crystal form A of LACE tosylate according to claims 7-9, comprising adding an anti-solvent to a solution of LACE tosylate, to crystallize LACE tosylate as crystal form A.~~

~~15. The method of claim 14, wherein the solution of LACE tosylate is at about 25 °C.~~

~~16. A crystal form A of LACE tosylate, made by adding an anti-solvent to a solution of LACE tosylate, to crystallize LACE tosylate as crystal form A, optionally, wherein the solution of LACE tosylate is at about 25 °C.~~

~~17. A method of preparing a crystal form B of LACE tosylate according to claims 10-12, comprising cooling a solution or suspension of LACE tosylate to lower than 10 °C, to crystallize LACE tosylate as crystal form B.~~

~~18. The method according to claim 17, comprising cooling a solution or suspension of LACE tosylate to lower than 4 °C, to crystallize LACE tosylate as crystal form B.~~

~~19. A crystal form B of LACE tosylate, made by cooling a solution or suspension of LACE tosylate to lower than 4 °C.~~

~~20.~~10. A crystal form of lipoic acid choline ester besylate characterized by an X ray diffraction pattern having three or more peaks at 2θ values selected from 4.3, 12.7, 18.4, 19.0, 19.9, 20.6, 20.8, 21.3, 23.3, 24.2, 25.5, 27.6, 31.4, 33.2, 35.0, 35.4 ± 0.2 °2θ.

~~21. A crystal form of lipoic acid choline ester 3,4-dihydroxy benzoate characterized by an X ray diffraction pattern having three or more peaks at 2θ values selected from 6.2, 10.8, 12.5, 14.5, 15.5, 16.7, 17.4, 18.0, 18.6, 19.6, 19.9, 21.9, 24.2, 25.1, 25.8, 26.8, 27.4, 31.7 ± 0.2 °2θ.~~

~~22. A method of preparing a lipoic acid choline ester (LACE) salt, comprising reacting LACE chloride with an alkali metal salt of an acid.~~

~~23. The method according to claim 22, wherein the alkali metal salt is a sodium or potassium salt.~~

~~24. The method according to claim 22, wherein the acid is an organic acid selected from the group consisting of benzenesulfonic acid, toluenesulfonic acid, and 3,4-dihydroxybenzoic acid.~~

~~25. The method according to any of claims 22-24, wherein the reacting is carried out in a suitable solvent.~~

~~26. The method according to claim 25, wherein the solvent is selected from the group consisting of acetone, acetonitrile, ethanol, and methanol.~~

~~27. The method according to any of claims 22-26, wherein the reacting is performed at temperatures of about 0 °C to about 30 °C, or about room temperature, or about 23 °C to about 25 °C.~~

~~28. A method of preparing lipoic acid choline ester (LACE) tosylate, comprising reacting LACE chloride with sodium tosylate in an anhydrous solvent selected from the group consisting of anhydrous acetone, anhydrous methanol, and anhydrous acetonitrile.~~

~~29. The method according to claim 28, wherein the anhydrous solvent is anhydrous acetone and the reaction is maintained at 25 °C for at least 24 hours, or at least 2, 3, 4, or 5 days.~~

~~30.~~11. A method of preparing lipoic acid choline ester ~~(LACE)~~ tosylate, comprising:

reacting lipoic acid with an activating agent, optionally in a solvent, and optionally in the presence of a base, to yield an activated lipoic acid intermediate, and

reacting the activated lipoic acid intermediate with choline tosylate, optionally in a solvent, and optionally in the presence of a base, to yield lipoic acid choline ester~~LACE~~ tosylate.

~~31.~~12. The method according to claim- 11~~30~~, with one or more of the following:

the activating agent is carbonyldiimidazole;

the reaction of lipoic acid with the activating agent is carried out in a solvent and the presence of a base;

the reaction of lipoic acid with an activating agent is carried out at temperatures below 25 °C;

the reaction of activated lipoic acid intermediate with the choline tosylate is carried out in a solvent and in the presence of a base; and

the reaction of activated lipoic acid intermediate with choline tosylate is carried out at temperatures below 25 °C, or below 30 °C.

~~32. The method according to any of claims 30-31, wherein lipoic acid imidazole intermediate is precipitated from the reaction by addition of an antisolvent and further isolated prior to reaction with the choline tosylate.~~

33. The method according to any of claims 30-32, with one or more of the following:
the reaction of lipoic acid with the activating agent is carried out in 2-methyltetrahydrofuran and the presence of N,N-diisopropylethylamine; and
the reaction of activated lipoic acid intermediate with the choline tosylate is carried out in a solvent selected from the group consisting of acetone, acetonitrile, or a mixture thereof, and in the presence of N,N-diisopropylethylamine.

34. The method according to any of claims 30-33, further comprising treating the LACE tosylate with activated charcoal, optionally wherein the LACE tosylate is dissolved in the solvent.

35. A method of preparing a crystalline form B of LACE tosylate, comprising
dissolving LACE tosylate in a first solvent,
adding a second solvent to the solution of LACE tosyate in the first solvent,
cooling the mixture of LACE tosylate, first solvent, and second solvent to temperatures below 10 °C,
to crystallize crystalline form B of LACE tosylate.

36. The method according to claim 35, wherein the first solvent is acetonitrile, ethanol, water, or mixtures thereof, and the second solvent is acetone, 2-butanone, methyl tert-butyl ketone, tetrahydrofuran, or mixtures thereof.

37. A LACE salt prepared by the method according to any of claims 22-27.

38. LACE tosylate, prepared by the method according to any of claims 22-36.

39. A method of preparing LACE besylate, comprising reacting LACE chloride with sodium besylate in a solvent selected from the group consisting of anhydrous acetone, anhydrous methanol, and anhydrous acetonitrile.

40. A method of preparing LACE 3,4-dihydroxybenzoate, comprising reacting LACE chloride with sodium 3,4-dihydroxybenzoate in solvent selected from the group consisting of anhydrous acetone, anhydrous methanol, or anhydrous acetonitrile.

41. The method according to claims 39 or 40, wherein the reacting is carried out at 25 °C for at least 24 hours, or at least 2, 3, 4, or 5 days.

~~42.~~13. A pharmaceutical composition, comprising an effective amount of lipoic acid choline ester tosylate or lipoic acid choline ester besylate, according to any of claims 0-~~4~~10, and a pharmaceutically acceptable excipient.

~~43. The pharmaceutical composition according to claim 42, comprising the lipoic acid choline ester tosylate in substantially pure form.~~

~~44. The pharmaceutical composition according to claim 43, wherein the lipoic acid choline ester tosylate is present in amounts of at least 90%, at least 92%, or at least 95% of the total LACE salts in the composition.~~

~~45. The pharmaceutical composition according to claim 42, comprising the lipoic acid choline ester besylate in substantially pure form.~~

~~46. The pharmaceutical composition according to claim 45, wherein the lipoic acid choline ester besylate is present in amounts of at least 90%, at least 92%, or at least 95% of the total LACE salts in the composition.~~

~~47. The pharmaceutical composition according to any of claims 42-45, formulated for ocular use.~~

~~48. The pharmaceutical composition according to any of claims 42-47, wherein the lipoic acid choline ester is in solution.~~

~~49. The pharmaceutical composition according to any of claims 42-48, for use in the treatment of presbyopia.~~

~~50.~~14. A pharmaceutical composition, comprising:

a lipoic acid choline ester tosylate or lipoic acid choline ester besylate~~salt~~, according to any of claims 1-10,

hydroxypropyl-β-cyclodextrin,

optionally, a tonicity agent,

optionally, a viscosity modifying agent,

optionally, a buffer, and

optionally, a preservative.

~~51.~~15. The pharmaceutical composition according to claim- 14~~50~~, comprising

about 0.5% w/v to about 5% w/v (based on the lipoic acid choline ester) of the lipoic acid choline ester salt,

about 1.5% w/v to about 25% w/v of hydroxypropyl-β-cyclodextrin,

up to 300 mM of a tonicity agent,

0% w/v to about 20% w/v of a viscosity modifying agent,

0% w/v to about 1% w/v of a buffer, and

0% w/v to about 0.5% w/v of a preservative.

~~52. The pharmaceutical composition according to claim 50 or 51, wherein the lipoic acid choline ester salt is lipoic acid choline ester tosylate, lipoic acid choline ester iodide, lipoic acid choline ester besylate or lipoic acid choline ester chloride.~~

~~53. The pharmaceutical composition according to any of claims 50-52, wherein the lipoic acid choline ester salt is lipoic acid choline ester tosylate.~~

~~54.~~16. The pharmaceutical composition according to any of claims 13-15~~50-53~~, comprising about 0.01% w/v to about 20% w/v of a viscosity modifying agent.

~~55. The pharmaceutical composition according to claim 54, wherein the viscosity modifying agent is selected from the group consisting of polyethylene glycols, cellulosic agents, and mixtures thereof.~~

~~56.~~17. The pharmaceutical composition according to claim- 16~~55~~, wherein the viscosity modifying agent is selected from the group consisting of cellulosic agents and is present in an amount of about 0.01% w/v to about 1% w/v.

~~57.~~ The pharmaceutical composition according to claim- 17~~56~~, wherein the viscosity modifying agent comprises or is substantially all hydroxypropylmethyl cellulose.

~~58.~~18. ~~The pharmaceutical composition according to any of claims 50-57, comprising about 1 mM to about 300 mM of a tonicity agent selected from the group consisting of ionic tonicity agents, nonionic tonicity agents, and mixtures thereof.~~

~~59.~~19. The pharmaceutical composition according to claim- 18~~58~~, comprising about 1 mM to about 150 mM of a tonicity agent selected from the group consisting of sodium chloride,

potassium chloride, and mixtures thereof, or about 1 mM to about 300 mM of a tonicity agent selected from the group consisting of mannitol, dextrose, and mixtures thereof.

~~60. The pharmaceutical composition according to claim 58, wherein the tonicity agent selected from the group consisting of sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof.~~

~~61.~~20. The pharmaceutical composition according to claim ~~59~~ 19~~60~~, wherein the tonicity agent comprises or is substantially all sodium chloride.

~~62.~~21. The pharmaceutical composition according to any of claims 13-20~~50-61~~, comprising about 0.01% w/v to about 1% w/v of a buffer.

~~63.~~22. The pharmaceutical composition according to claim ~~59~~ 21~~61~~, wherein the buffer is selected from the group consisting of phosphate buffers (e.g., sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous), acetate buffer, citrate buffer, borate buffers, and HBSS (Hank's Balanced Salt Solution).

~~64.~~23. The pharmaceutical composition according to claim 21~~63~~ wherein the buffer comprises or is substantially all acetate buffer.

~~65.~~24. The pharmaceutical composition according to any of claims 13-23~~50-64~~, comprising 0% w/v to about 0.5% w/v of a preservative selected from the group consisting of benzalkonium chloride, sorbic acid, boric acid, and mixtures thereof.

~~66.~~25. The pharmaceutical composition according to any of claims 13-24~~50-65~~, having a pH of about 4.3 to about 4.7.

~~67.~~26. The pharmaceutical composition according to any of claims 13-25~~50-65~~, wherein the pharmaceutical composition does not include a biochemical energy source.

~~68.~~27. The pharmaceutical composition according to any of claims 13-26~~50-67~~, wherein the pharmaceutical composition does not include benzalkonium chloride.

~~69.~~28. The pharmaceutical composition according to any of claims 13-27~~50-68~~, wherein the pharmaceutical composition does not include a preservative and wherein the pharmaceutical composition meets US Pharmacopoeia preservation standards for sterile parenteral multi-dose compositions.

~~70.~~29. The pharmaceutical composition according to any of claims 13-28~~50-69~~, comprising hydroxypropyl-β-cyclodextrin in an amount about equimolar to the lipoic acid choline ester salt or about 1.5% w/v, about 2.5% w/v, about 3.2% w/v, about 3.3% w/v, about 6.3% w/v, about 6.7% w/v, about 11.2% w/v, about 11.5% w/v, about 15.0% w/v, or about 19.6% w/v of hydroxypropyl-β-cyclodextrin.

~~71.~~ 30. The pharmaceutical composition according to any of claims 13-29~~50-70~~, having an osmolality of about 250 mOsm to about 425 mOsm.

~~72. A pharmaceutical composition, comprising:~~

~~about 0.5% w/v, about 1.3% w/v, about 2.3% w/v, about 3% w/v, or about 4% w/v (based on the lipoic acid choline ester) of lipoic acid choline ester tosylate,~~

~~hydroxypropyl β-cyclodextrin in an amount about equimolar to the lipoic acid choline ester,~~

~~about 0.1% w/v to about 1% w/v of sodium chloride,~~

~~about 0.1% w/v to about 0.75% w/v of hydroxypropylmethyl cellulose, and~~

~~about 0.01% w/v to about 0.5% w/v of acetate buffer,~~

~~wherein the pharmaceutical composition has a pH of about 4.3 to about 4.7,~~

~~wherein the pharmaceutical composition has an osmolality of about 250 mOsm to about 425 mOsm,~~

~~wherein the pharmaceutical composition does not include a preservative and does not include alanine, and~~

~~wherein the pharmaceutical composition meets US Pharmacopoeia preservation standards for sterile parenteral multi-dose compositions.~~

~~73. The pharmaceutical composition according to claim 72, comprising about 1.5% w/v, about 2.5% w/v, about 3.2% w/v, about 3.3% w/v, about 6.3% w/v, about 6.7% w/v, about 11.2% w/v, about 11.5% w/v, about 15.0% w/v, or about 19.6% w/v of hydroxypropyl β-cyclodextrin.~~

~~74. The pharmaceutical composition according to any of claims 50-73, wherein the pharmaceutical composition is a sterile, aqueous solution.~~

~~75. The pharmaceutical composition according to any of claims 50-74, wherein the lipoic acid choline ester salt is substantially all (R) lipoic acid choline ester salt.~~

~~76. A method of preparing a pharmaceutical composition according to any of claims 50-75, comprising:~~

~~adding to water an amount of lipoic acid choline ester salt and hydroxypropyl-beta-cyclodextrin to prepare a solution of lipoic acid choline ester and hydroxypropyl-beta-cyclodextrin,~~

~~optionally adding a tonicity agent, a viscosity modifying agent, a buffer, and a preservative to the solution of lipoic acid choline ester and hydroxypropyl-beta-cyclodextrin,~~

~~adjusting the pH with an acid or base,~~

~~optionally adding water to adjust the concentration of LACE salt to the final concentration, and~~

~~optionally sterilizing the solution to provide the pharmaceutical composition.~~

~~77.~~ A lipoic acid choline ester for use ~~A pharmaceutical composition prepared by the process of claim 76.~~

~~78. A method for treating or preventing a disease or disorder associated with oxidative damage, comprising ocularly administering to a patient a pharmaceutical composition according to any of claims 50-75.~~

~~79.~~31. in~~A method for~~ treating or preventing a disease or disorder associated with oxidative damage, ~~comprising ocularly administering to a patient~~ wherein a lipoic acid choline ester salt at a total daily dose of about 0.1 mg to about 5 mg of lipoic acid choline ester, about 0.2 mg to about 3 mg of lipoic acid choline ester, about 0.4 mg to about 2.5 mg of lipoic acid choline ester, or of about 0.2 mg, about 0.4 mg, about 0.5 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 1.1 mg, about 1.2 mg, about 1.4 mg, about 1.5 mg, about 1.6 mg, about 2.1 mg, about 2.4 mg, about 2.8 mg, or about 3.2 mg, of lipoic acid choline ester is to be ocularly administered to a patient, and

wherein the lipoic acid choline ester is in a salt form selected from the group consisting of lipoic acid choline ester tosylate, lipoic acid choline ester besylate, lipoic acid choline ester chloride or lipoic acid choline ester iodide.

~~80.~~32. The lipoic acid choline ester~~method~~ for use according to claim ~~-31~~79, wherein the lipoic acid choline ester is to be administered to the patient in the form of a pharmaceutical composition according to any of claims 13-30~~50-75~~.

~~81.~~ 33. The lipoic acid choline ester~~method~~ for use according to claim 32~~-78~~, wherein ~~comprising ocularly administering to the patient~~ a total daily dose of lipoic acid choline ester tosylate of about 0.2 mg to about 7 mg, or about 0.5 mg to about 5 mg, or about 0.7 mg to about 3.5 mg, or about 0.3 mg, about 0.6 mg, about 0.8 mg, about 1.0 mg, about 1.5 mg, about 1.7 mg, about 2.0 mg, about 2.2 mg, about 2.3 mg, about 2.5 mg, about 2.6 mg, about 3.0 mg, about 3.4, about 3.9, about 4.5, about 5.0, about 6.0, or about 6.7 mg is to be ocularly administered to a patient.

~~82~~ 34. A ~~method~~ lipoic acid choline ester for use in~~of~~ improving distance corrected near vision acuity (DCNVA) in a subject in need thereof, ~~comprising ocularly administering~~wherein an effective amount of a pharmaceutical composition according to any of claims 13-30~~50-75~~ is to be ocularly administered to a patient to the subject.

~~83. The method of claim 82, wherein the DCNVA is improved by at least 1 letter, at least 2 letters, at least 3 letters, at least 4 letters, or at least 5 letters.~~

~~84. A method of increasing the accommodative amplitude of a lens by at least 0.1 diopters (D) in a subject in need thereof, comprising ocularly administering an effective amount of a pharmaceutical composition according to any of claims 50-75 to the subject.~~

~~85. The method according to claim 84, wherein the accommodative amplitude of the lens is increased by at least 0.2, 0.5, 1, 1.2, 1.5, 1.8, 2, 2.5, 3, or 5 diopters.~~

~~86~~ 35. The lipoic acid choline ester for use ~~method~~ of any of claims 31-34~~82-85~~, wherein the subject suffers from a disease or disorder associated with oxidative damage.

~~87.~~ 36. The lipoic acid choline ester for use ~~method~~ of any of claims ~~78-81~~31-35~~ or 86~~, wherein the disease or disorder associated with oxidative damage is presbyopia or cataract.

~~88. The pharmaceutical compositions according to any of claims 50-75, meeting one or more of the following conditions:~~

~~wherein the pharmaceutical composition comprises at least 95%, at least 96%, at least 97%, or at least 98% of the initial amount of lipoic acid choline ester after storage at 25 °C for 10 weeks;~~

~~wherein the pharmaceutical composition comprises at least 95%, at least 96%, at least 97%, or at least 98% of the initial amount of lipoic acid choline ester after storage at 25 °C for 13 weeks; or~~

~~wherein the pharmaceutical composition comprises at least 80%, at least 85%, at least 86%, at~~

least 87%, or at least 88% of the initial amount of lipoic acid choline ester after storage at 40 °C for 13 weeks.

89. The pharmaceutical composition according to any of claims 54-53, 58-71, 74, and 75, when administered to a rabbit, results in a maximum aqueous humor lipoic acid concentration (Cmax) that is at least 2 times, at least 2.5 times, at least 3 times, at least 3.5 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times the aqueous humor lipoic acid concentration of an pharmaceutical composition that does not include a viscosity modifying agent.

90. The pharmaceutical composition according to any of claims 50-75, when administered to a rabbit, results in a maximum corneal lipoic acid concentration (Cmax) that is at least 2 times, at least 2.5 times, at least 3 times, at least 3.5 times, at least 4 times, at least 5 times, at least 6 times, at least 7 times, at least 8 times, at least 9 times, or at least 10 times the aqueous humor lipoic acid concentration of a pharmaceutical composition that includes a viscosity modifying agent.

91. The pharmaceutical composition according to any of claims 50-75, that include less than about 2 %, less than about 1 %, less than about 0.5 %, less than about 0.4% , less than about 0.3%, less than about 0.2% or less than about 0.1% of associative species of LACE, when measured in terms of HPLC peak area relative to LACE.