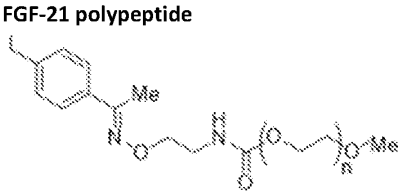
WHAT IS CLAIMED IS:

1. A pharmaceutical formulation comprising (i) a fibroblast growth factor 21 (FGF-21) polypeptide conjugated to a polyethylene glycol (PEG) moiety ("FGF-21 conjugate") and (ii) an aminopolycarboxylic acid cation chelator, wherein the formulation has improved stability compared to a reference formulation that does not contain the aminopolycarboxylic acid cation chelator, wherein the FGF-21 conjugate comprises formula I:



(Formula I), and wherein n is any integer.

2. The pharmaceutical formulation of claim 1, wherein the PEG moiety is conjugated to a non-natural amino acid in the FGF-21 polypeptide.

3. The pharmaceutical formulation of claim 1 or 2, wherein the non-natural amino acid in the FGF-21 polypeptide is a phenylalanine derivative.

4. The pharmaceutical formulation of claim 3, wherein the phenylalanine derivative is para-acetyl-L-phenylalanine.

5. The pharmaceutical formulation of any one of claims 1 to 4, wherein the FGF-21 polypeptide comprises an amino acid sequence having at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity to the amino acid sequence of SEQ ID NO: 3, wherein the polypeptide has a FGF-21 activity.

6. The pharmaceutical formulation of any one of claims 2 to 5, wherein the non-natural amino acid is at amino acid residue 109 corresponding to SEQ ID NO: 3.

7. The pharmaceutical formulation of any one of claims 1 to 6, wherein the FGF-21 polypeptide comprises the sequence as set forth in SEQ ID NO: 1.

8. The pharmaceutical formulation of any one of claims 1 to 7, wherein the FGF-21 conjugate corresponds to a compound of SEQ ID NO: 2.

9. The pharmaceutical formulation of any one of claims 1 or 8, wherein the n is from about 500 to about 900 ethylene glycol units, from about 600 to about 800 ethylene glycol units, from about 650 to about 750 ethylene glycol units, or from about 670 to about 690.

10. The pharmaceutical formulation of any one of claims 1 to 9, wherein the n is between about 670 and about 690, e.g., about 681.

11. The pharmaceutical formulation of any one of claims 1 to 10, wherein the FGF-21 conjugate corresponds to a compound of SEQ ID NO: 4.

12. The pharmaceutical formulation of claims 1 to 11, wherein the FGF-21 conjugate is in an L conformation.

13. The pharmaceutical formulation of any one of claims 1 to 12, wherein the FGF-21 conjugate is present at a concentration between about 1 mg/ml and about 40 mg/ml.

14. The pharmaceutical formulation of claim 13, wherein the FGF-21 conjugate is present at a concentration of about 10 mg/ml or about 20 mg/ml.

15. The pharmaceutical formulation of claim 14, wherein the FGF-21 conjugate is present at a concentration of about 20 mg/ml.

16. The pharmaceutical formulation of any one of claims 1 to 15, wherein the FGF-21 conjugate is present in an amount between about 1 mg and about 40 mg per unit dose.

17. The pharmaceutical formulation of claim 16, wherein the FGF-21 conjugate is present in an amount of about 1 mg per unit dose, about 5 mg per unit dose, about 10 mg per unit dose, about 20 mg per unit dose, or about 40 mg per unit dose.

18. The pharmaceutical formulation of claim 16, wherein the FGF-21 conjugate is present in an amount of about 10 mg or about 20 mg per unit dose.

19. The pharmaceutical formulation of any one of claims 1 to 18, which exhibits one or more of:

(a) a lower rate of polypeptide deamidation when stored at 40 ºC for about a month with respect to the reference formulation;

(b) a lower rate of high molecular weight (HMW) polypeptide aggregation when stored at 40 ºC for about a month with respect to the reference formulation; or

(c) both (a) and (b).

20. The pharmaceutical formulation of any one of claims 1 to 19, wherein the aminopolycarboxylic acid cation chelator prevents or mitigates oxidation of one or more methionines.

21. The pharmaceutical formulation of claim 20, wherein the methionines correspond to Met1 and/or Met169 of the FGF-21 polypeptide.

22. The pharmaceutical formulation of any one of claims 20 or 21, wherein methionine oxidation is prevented or mitigated at 25 ºC and/or 40 ºC.

23. The pharmaceutical formulation of any one of claim 1 to 22, wherein the aminopolycarboxylic acid cation chelator is diethylenetriaminepentaacetic acid (DTPA).

24. The pharmaceutical formulation of any one of claims 1 to 23, wherein the DTPA cation chelator is present in an amount between about 10 μM and about 100 μM DTPA, between about 20 μM and about 90 μM DTPA, between about 30 μM and about 80 μM DTPA, between about 25 μM and about 75 μM DTPA, or between about 40 μM and about 60 μM DTPA, or between about 30 μM and about 70 μM DTPA, or between about 40 μM and about 70 μM DTPA.

25. The pharmaceutical formulation of claims 23 or 24, wherein the DTPA cation chelator is present in an amount of about 40 μM, about 45 μM, about 50 μM, about 55 μM, or about 60 μM DTPA.

26. The pharmaceutical formulation of any one of claims 1 to 25, wherein the pH is above 6.5, above 6.6, above 6.7, above 6.8, above 6.9, above 7.0, above 7.1, above 7.2, above 7.3, above 7.4, or above 7.5.

27. The pharmaceutical formulation of claim 26, wherein the pH is between about 6.7 and about 7.5, about 6.8 and about 7.5, about 6.9 and about 7.4, about 7.0 and about 7.3, about 7.1 and 7.2, about 7.1 and about 7.3, about 7.1 and about 7.4, or about 7.1 and about 7.5.

28. The pharmaceutical formulation of claim 27, wherein the pH is about 6.7, about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, or about 7.5.

29. The pharmaceutical formulation of any one of claims 26 to 28, wherein the pharmaceutical formulation is more stable than a reference formulation with a pH of 6.5.

30. The pharmaceutical formulation of any one of claims 1 to 29, further comprising a surfactant.

31. The pharmaceutical formulation of claim 30, wherein the surfactant is a nonionic surfactant.

32. The pharmaceutical formulation of claim 31, wherein the nonanionic surfactant is a polysorbate.

33. The pharmaceutical formulation of claim 32, wherein the polysorbate is polyoxyethylene (20) sorbitan monooleate (polysorbate 80).

34. The pharmaceutical formulation of claim 33, wherein the polysorbate 80 surfactant is present in an amount of about 0.01% to about 0.1% (w/v), about 0.02% to about 0.09% (w/v),

about 0.03% to about 0.08% (w/v), about 0.04% to about 0.07% (w/v), or about 0.05% to about 0.06% (w/v).

35. The pharmaceutical formulation of claim 33 or 34, wherein the polysorbate 80 surfactant is present in an amount of at least about 0.01% (w/v), at least about 0.02% (w/v), at least about 0.03% (w/v), at least about 0.04% (w/v), at least about 0.05% (w/v), at least about 0.06% (w/v), at least about 0.07% (w/v), at least about 0.08% (w/v), at least about 0.09% (w/v) or at least about 0.1% (w/v).

36. The pharmaceutical formulation of any one of claims 30 to 35, wherein the surfactant mitigates particulate and/or air bubble formation when agitated on a shaker.

37. The pharmaceutical formulation of any one of claims 1 to 36, further comprising an amino acid buffering agent.

38. The pharmaceutical formulation of claim 37, wherein the amino acid buffering agent is histidine.

39. The pharmaceutical formulation of claim 38, wherein the histidine buffering agent is present in an amount of about 10 mM to about 100 mM histidine, about 20 mM to about 90 mM histidine, about 30 mM to about 80 mM histidine, about 40 mM to about 70 mM histidine, about 10 mM to about 30 mM histidine, about 15 mM to about 25 mM histidine, about 17.5 to about 22.5 histidine, or about 40 mM to about 60 mM histidine.

40. The pharmaceutical formulation of claim 38 or 39, wherein the histidine buffering agent is present in an amount of about 10 mM histidine, about 15 mM histidine, about 20 mM histidine, about 25 mM histidine, about 30 mM histidine, about 35 mM histidine, about 40 mM histidine, about 45 mM histidine or about 50 mM histidine.

41. The pharmaceutical formulation of any one of claims 1 to 40, further comprising an osmotic regulator.

42. The pharmaceutical formulation of claim 41, wherein the osmotic regulator comprises a sugar.

43. The pharmaceutical formulation of claim 42, wherein the sugar is sucrose.

44. The pharmaceutical formulation of claim 43, wherein the sucrose osmotic regulator is present in an amount of about 100 mM to about 1 M sucrose, about 200 mM to about 900 mM, about 300 mM to about 800 mM, about 400 mM to about 700 mM, or about 500 mM to about 600 mM.

45. The pharmaceutical formulation of claim 43 or 44, wherein the sucrose osmotic regulator is present in an amount of about 100 mM sucrose, about 200 mM sucrose, about 300 mM sucrose, about 400 mM sucrose, about 500 mM sucrose, about 600 mM sucrose, about 700 mM sucrose, about 800 mM sucrose, about 900 mM sucrose, or about 1M sucrose.

46. The pharmaceutical formulation of any one claims 1 to 45, wherein the formulation is formulated for subcutaneous administration.

47. The pharmaceutical formulation of claim 46, wherein the formulation is formulated for subcutaneous administration with a safety syringe.

48. The pharmaceutical formulation of any one of claim 1 to 47, wherein the formulation is formulated for daily or weekly administration.

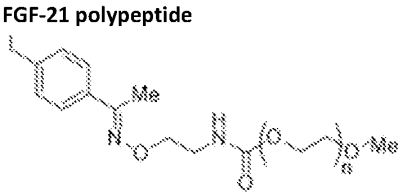
49. The pharmaceutical formulation of any one of claims 1 to 48, wherein the formulation is an aqueous formulation.

50. A pharmaceutical formulation comprising:
(i) a FGF-21 conjugate;
(ii) histidine at a concentration between about 10 mM and about 50 mM;
(iii) sucrose at a concentration between about 100 mM and about 1M;
(iv) Polysorbate 80 at a concentration between about 0.01% and about 0.1% (w/v); and,

(v) DTPA at a concentration between about 10 μM and about 100 μM;

wherein the pH of the formulation is between about 6.7 and about 7.5,

wherein the FGF-21 conjugate comprises formula I:



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

51. A pharmaceutical formulation comprising:

(i) a FGF-21 conjugate;

(ii) histidine at a concentration of about 20 mM;

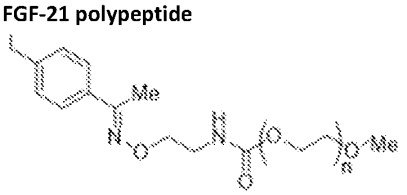
(iii) sucrose at a concentration of about 600 mM;

(iv) Polysorbate 80 at a concentration of about 0.05% (w/v); and

(v) DTPA at a concentration of about 50 μM;

wherein the pH is about 7.1,

wherein the FGF-21 conjugate comprises formula I:



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

52. A pharmaceutical formulation comprising:

(i) a FGF-21 conjugate;

(ii) histidine at a concentration of 20 mM;

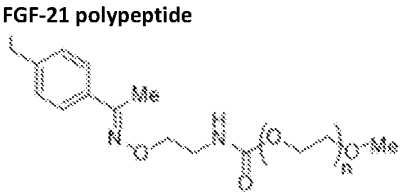
(iii) sucrose at a concentration of 600 mM;

(iv) Polysorbate 80 at a concentration of 0.05% (w/v); and

(v) DTPA at a concentration of 50 μM;

wherein the pH is 7.1,

wherein the FGF-21 conjugate comprises formula I:



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

53. A pharmaceutical formulation comprising:

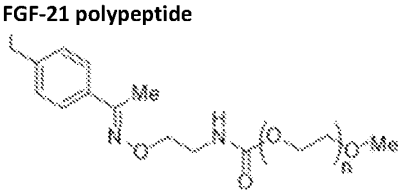
(i) a FGF-21 conjugate;

(ii) histidine at a concentration of about 20 mM; and

(iii) sucrose at a concentration of about 600 mM;

wherein the pH is about 7.0,

wherein the FGF-21 conjugate comprises formula I:



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

54. A pharmaceutical formulation comprising:

(i) a FGF-21 conjugate;

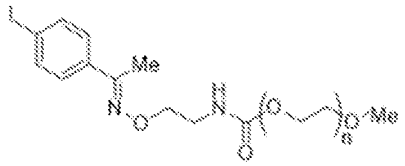
(ii) histidine at a concentration of 20 mM; and

(iii) sucrose at a concentration of 600 mM;

wherein the pH is 7.0,

wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

55. A pharmaceutical formulation comprising:

(i) FGF-21 conjugate at a concentration of about 10 mg/mL;

(ii) histidine at a concentration of about 20 mM;

(iii) sucrose at a concentration of about 600 mM;

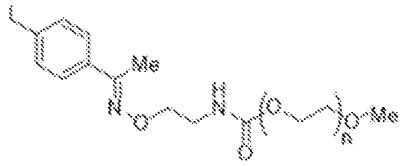
(iv) Polysorbate 80 at a concentration of about 0.05% (w/v); and

(v) DTPA at a concentration of about 50 uM;

wherein the pH is about 7.1,

wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

56. A pharmaceutical formulation comprising:

(i) FGF-21 conjugate at a concentration of about 20 mg/mL;

(ii) histidine at a concentration of about 20 mM;

(iii) sucrose at a concentration of about 600 mM;

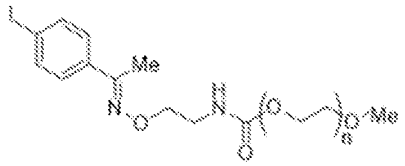
(iv) Polysorbate 80 at a concentration of about 0.05% (w/v); and

(v) DTPA at a concentration of about 50 uM;

wherein the pH is about 7.1,

wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

57. A pharmaceutical formulation comprising:

(i) FGF-21 conjugate at a concentration of 10 mg/mL;

(ii) histidine at a concentration of 20 mM;

(iii) sucrose at a concentration of 600 mM;

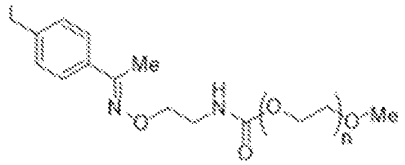
(iv) Polysorbate 80 at a concentration of 0.05% (w/v); and

(v) DTPA at a concentration of 50 uM;

wherein the pH is 7.0,

wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

58. A pharmaceutical formulation comprising:

(i) PEG-FGF21 of SEQ ID NO: 2 or 4 at a concentration of 20 mg/mL;

(ii) histidine at a concentration of 20 mM;

(iii) sucrose at a concentration of 600 mM;

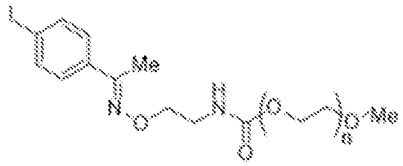
(iv) Polysorbate 80 at a concentration of 0.05% (w/v); and

(v) DTPA at a concentration of 50 uM;

wherein the pH is 7.0,

wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide

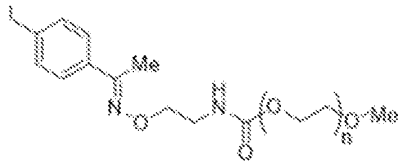


(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

59. A method to improve the stability of a pharmaceutical formulation comprising a fibroblast growth factor 21 (FGF-21) polypeptide conjugated to a polyethylene glycol (PEG) moiety ("FGF-21 conjugate"), the method comprising admixing an aminopolycarboxylic acid cation chelator, wherein the formulation has improved stability compared to a reference formulation that does not contain the aminopolycarboxylic acid cation chelator,
wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

60. The method of claim 59, wherein the PEG moiety is conjugated to a non-natural amino acid in the FGF-21 polypeptide.

61. The method of claim 60, wherein the non-natural amino acid in the FGF-21 polypeptide is para-acetyl-L-phenylalanine.

62. The method of any one of claims 59 to 61, wherein the FGF-21 polypeptide is a FGF-21 polypeptide of SEQ ID NO: 1.

63. The method of any one of claims 59 to 62, wherein the FGF-21 conjugate is in an L conformation.

64. The method of any one of claims 59 to 63, wherein the improvement in stability comprises (i) an increase in polypeptide physical stability, (ii) an increase in polypeptide chemical stability, or (iii) both (i) and (ii).

65. The method of claim 64, wherein the increase in physical stability comprises (i) prevention or decrease of polypeptide aggregation, (ii) prevention or decrease of polypeptide fragmentation, or (iii) both (i) and (ii).

66. The method of claim 65, wherein the increase in chemical stability comprises (i) prevention or decrease of polypeptide deamidation, (ii) prevention or decrease of polypeptide oxidation, or (iii) both (i) and (ii).

67. The method of any one of claims 59 to 66, wherein the improvement in stability comprises one or more of:
(a) a lower rate of polypeptide deamidation when stored at 40 °C for about a month with respect to the reference formulation;
(b) a lower rate of high molecular weight (HMW) polypeptide aggregation when stored at 40 °C for about a month with respect to the reference formulation; or
(c) both (a) and (b).

68. The method of any one of claims 59 to 67, wherein the improvement in stability comprises preventing or mitigating oxidation of one or more methionines.

69. The method of claim 68, wherein the methionines correspond to Met1 and/or Met169 of the FGF-21 polypeptide.

70. The method of any one of claims 68 or 69, wherein methionine oxidation is prevented or mitigated at 25 °C and/or 40 °C.

71. The method of any one of claims 59 to 70, wherein the aminopolycarboxylic acid cation chelator is DTPA.

72. The method of claim 71, wherein the DTPA cation chelator is present in an amount between about 10 μM and about 100 μM DTPA, between about 20 μM and about 90 μM DTPA, between about 25 μM and about 75 μM DTPA, between about 40 μM and about 60 μM DTPA, between about 30 μM and about 70 μM DTPA, between about 30 μM and about 80 μM DTPA, or between about 40 μM and about 70 μM.

73. The method of claim 71 or 72, wherein the DTPA cation chelator is present in an amount of about 40 μM, about 45 μM, about 50 μM, about 55 μM, or about 60 μM DTPA.

74. The method of any one of claims 59 to 73, further comprising adjusting the pH to above 6.5, above 6.6, above 6.7, above 6.8, above 6.9, or above 7.0.

75. The method of claim 74, wherein the pH is adjusted to between about 6.8 and about 7.5, or between about 6.9 and about 7.4, or between about 7.0 and about 7.3, or between about 7.1 and 7.2, or between about 7.1 and about 7.3, or between about 7.1 and about 7.4, or between about 7.1 and about 7.5.

76. The method of claim 75, wherein the adjusted pH is about 6.8, about 6.9, about 7.0, about 7.1, about 7.2, about 7.3, about 7.4, or about 7.5.

77. The method of any one of claims 74 to 76, wherein the formulation is more stable than the reference formulation having a pH of 6.5.

78. The method of any one of claims 59 to 77, further comprising admixing a surfactant.

79. The method of claim 78, wherein the surfactant is a nonionic surfactant.

80. The method of claim 79, wherein the nonanionic surfactant is a polysorbate.

81. The method of claim 80, wherein the polysorbate is polysorbate 80.

82. The method of claim 81, wherein the polysorbate 80 surfactant is admixed in an amount of about 0.01% to about 0.1% (w/v), about 0.02% to about 0.09% (w/v), about 0.03% to about 0.08% (w/v), about 0.04% to about 0.07% (w/v), or about 0.05% to about 0.06% (w/v).

83. The method of claim 81 or 82, wherein polysorbate 80 surfactant is admixed in an amount of at least about 0.01% (w/v), at least about 0.02% (w/v), at least about 0.03% (w/v), at least about 0.04% (w/v), at least about 0.05% (w/v), at least about 0.06% (w/v), at least about 0.07% (w/v), at least about 0.08% (w/v), at least about 0.09% (w/v) or at least about 0.1% (w/v).

84. The method of any one of claims 79 to 83, wherein the surfactant mitigates particulate formation and/or air bubble formation when agitated on a shaker.

85. The method of any one of claims 59 to 84, further comprising admixing an amino acid buffering agent.

86. The method of claim 85, wherein the amino acid buffering agent is histidine.

87. The method of claim 86, wherein the histidine buffering agent is admixed in an amount of about 10 mM to about 100 mM histidine, about 20 mM to about 90 mM histidine, about 30 mM to about 80 mM histidine, about 40 mM to about 70 mM histidine, about 10 mM to about 30 mM histidine, about 15 mM to about 25 mM histidine, about 17.5 mM to about 22.5 mM histidine, or about 40 mM to about 60 mM histidine.

88. The method of claim 86 or 87, wherein the histidine buffering agent is admixed in an amount of about 10 mM histidine, about 15 mM histidine, about 20 mM histidine, about 25 mM histidine, about 30 mM histidine, about 35 mM histidine, about 40 mM histidine, about 45 mM histidine or about 50 mM histidine.

89. The method of any one of claims 59 to 88, further comprising admixing an osmotic regulator.

90. The method of claim 89, wherein the osmotic regulator comprises a sugar.

91. The method of claim 90, wherein the sugar is sucrose.

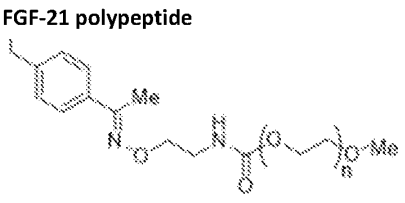
92. The method of claim 91, wherein the sucrose osmotic regulator is admixed in an amount of about 100 mM to about 1 M sucrose, about 200 mM to about 900 mM sucrose, about 300 mM to about 800 mM sucrose, about 400 mM to about 700 mM sucrose, or about 500 mM to about 600 mM sucrose.

93. The method of claim 91 or 92, wherein the sucrose osmotic regulator is admixed in an amount of about 100 mM sucrose, about 200 mM sucrose, about 300 mM sucrose, about 400 mM sucrose, about 500 mM sucrose, about 600 mM sucrose, about 700 mM sucrose, about 800 mM sucrose, about 900 mM sucrose, or about 1M sucrose.

94. The method of any one of claims 59 to 93, wherein the formulation is an aqueous formulation.

95. A pharmaceutical formulation prepared according to the method of any one of claims 59 to 94.

96. A vial comprising:
(i) a FGF-21 conjugate;
(ii) histidine at a concentration between about 10 mM and about 50 mM;
(iii) sucrose at a concentration between about 100 mM and about 1M;
(iv) Polysorbate 80 at a concentration between about 0.01% and about 0.1% (w/v); and,
(v) DTPA at a concentration between about 10 μM and about 100 μM;
wherein the pH of the formulation is between about 6.7 and about 7.5,
wherein the FGF-21 conjugate comprises formula I:



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

97. A vial comprising:

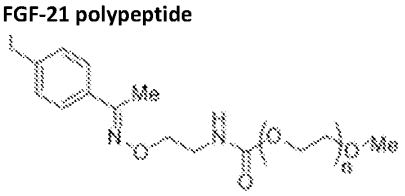
(i) about 5 mg to about 20 mg of a FGF-21 conjugate;

(ii) histidine at a concentration of about 20 mM; and

(iii) sucrose at a concentration of about 600 mM;

wherein the pH is about 7.0,

wherein the FGF-21 conjugate comprises formula I:



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

98. A vial comprising:

(i) about 10 mg to about 20 mg of a FGF-21 conjugate;

(ii) histidine at a concentration of about 20 mM;

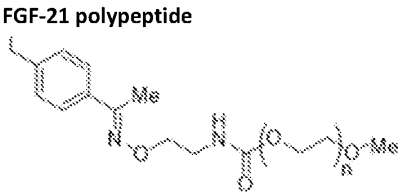
(iii) sucrose at a concentration of about 600 mM;

(iv) Polysorbate 80 at a concentration of about 0.05% (w/v); and

(v) DTPA at a concentration of about 50 uM;

wherein the pH is about 7.1,

wherein the FGF-21 conjugate comprises formula I:



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

99. A vial comprising:

(i) about 10 mg of a FGF-21 conjugate;

(ii) histidine at a concentration of about 20 mM;

(iii) sucrose at a concentration of about 600 mM;

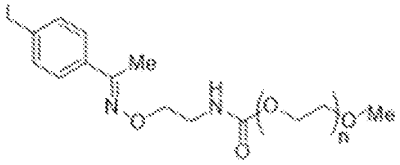
(iv) Polysorbate 80 at a concentration of about 0.05% (w/v); and

(v) DTPA at a concentration of about 50 uM;

wherein the pH is about 7.1,

wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

100. A vial comprising:

(i) about 20 mg of a FGF-21 conjugate;

(ii) histidine at a concentration of about 20 mM;

(iii) sucrose at a concentration of about 600 mM;

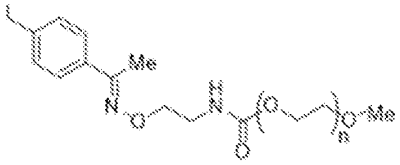
(iv) Polysorbate 80 at a concentration of about 0.05% (w/v); and

(v) DTPA at a concentration of about 50 uM;

wherein the pH is about 7.1,

wherein the FGF-21 conjugate comprises formula I:

FGF-21 polypeptide



(Formula I),

wherein n is between about 670 and about 690, e.g., about 681, and wherein the FGF-21 polypeptide comprises SEQ ID NO: 1.

101. A kit or article of manufacture comprising (i) the pharmaceutical formulation of any one of claims 1 to 58, and 95 or the vial of any one of claims 96 to 100, and (ii) instructions for use.

102. A method of treating or preventing a disease or condition associated with fibrosis and/or diabetes in a subject in need thereof comprising administering to the subject an effective amount of a pharmaceutical formulation of any one of claims 1 to 58 and 95, the vial of any one of claims 96 to 100, and the kit of claim 101.

103. The method of claim 102, wherein the disease or condition is diabetes.

104. The method of claim 103, wherein the diabetes is type 2 diabetes.

105. The method of claim 102, wherein the disease or condition is nonalcoholic steatohepatitis (NASH).

106. The method of any one of claims 102 to 105, wherein administration of the effective amount of the pharmaceutical formulation to the subject decreases liver stiffness, decreases percentage body fat, decreases body weight, decreases liver-to-body weight ratio, decreases liver lipid content, decreases liver fibrosis area, decreases fasting blood glucose levels, decreases fasting triglyceride levels, decreases LDL cholesterol levels, decreases ApoB levels, decreases ApoC levels, increases HDL cholesterol, or any combination thereof.

107. The method of any one of claims 102 to 106, wherein the FGF-21 conjugate is administered at a flat dose of about 20 mg.

108. The method of claim 107, wherein the FGF-21 conjugate is administered at a dosing interval of a week.

109. The method of any one claims 102 to 108, wherein the pharmaceutical formulation is administered subcutaneously.

110. The method of claim 109, wherein the pharmaceutical formulation is administered subcutaneously using a safety syringe.

111. The method of any one of claims 102 to 110, wherein the administration of the pharmaceutical formulation to the subject results in

(i) reduction in levels of liver fat;

(ii) reduction in levels of liver injury;

(iii) reduction in levels of fibrosis;

(iv) decrease in levels of fibrosis biomarker serum Pro-C3 (N-terminal type III collagen propeptide);

(v) decrease in levels of alanine aminotransferase (ALT);

(vi) decrease in levels of aspartate aminotransferase (AST),

(vii) increase in levels of serum adiponectin;

(viii) decrease in levels of plasma LDL

(ix) increase in levels of plasma HDL;

(x) decrease in levels of plasma triglyceride;

(xi) reduction in level of liver stiffness; or

(xii) any combination thereof,

compared to the levels in untreated subjects or to the subject prior to the administration of the pharmaceutical formulation.