US Patent No. 9,938,335 generally describes dual GLP-1/glucagon receptor agonist peptides administered by parenteral routes. The compound described in Example 2 of US Patent No. 9,938,335 has the sequence provided in SEQ ID NO: 1 (hereinafter referred to as Compound 1). Compound 1 is currently being evaluated for the treatment of patients with type 2 diabetes. Compound 1 is a synthetic peptide composed of thirty-four amino acid residues, one non-coded amino acid (aminoisobutyric acid (Aib)), a C-terminal amide, and a C20 fatty di-acid moiety covalently attached at lysine 20 in the sequence. The covalent linker comprises a gamma-glutamate and two PEG units. Therapeutically, the peptide is an oxyntomodulin-like acylated peptide with dual agonist activity of human glucagon-like peptide (GLP-1) and glucagon (Gcg). It independently binds and activates both the glucagon-like peptide receptor (GLP-1R) and the glucagon receptor (GcgR) on the surface of susceptible cells.

It has surprisingly been found that the compounds described in US Patent No. 9,938,335, particularly Compound 1, have sub-optimal solubility at lower pH values (e.g. pH 5.0 to 6.5). It also been found that the compounds described in US Patent No. 9,938,335, particularly Compound 1, have sub-optimal stability in certain formulations having pH values of 7.0 – 8.5. Pharmaceutical formulations comprising a dual GLP-1/glucagon receptor agonist peptide compound having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 or SEQ ID NO: 4 are needed that avoid these observed problems.

The pharmaceutical formulations provided herein satisfy the aforementioned needs. More particularly, the pharmaceutical formulations provided herein are suitable for SQ, IM and/or IP administration of dual GLP-1/glucagon receptor agonist peptides while preserving the functional characteristics of the peptide essential for therapeutic efficacy.

SUMMARY

In an aspect of the present disclosure, there is provided a pharmaceutical formulation comprising:

(i) a compound of the following formula

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with a C14-C24 fatty acid via a linker between the Lys at position 20 and the C14-C24 fatty acid, wherein the linker is ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)t, wherein t is 1 or 2; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 5);

(ii) a buffer;

(iii) a tonicity agent; and

(iii) an antioxidant,

wherein the pH of the formulation is 7.8 - 9.0.

In another aspect of the present disclosure, there is provided a pharmaceutical formulation as disclosed herein for use in the treatment and/or prevention of type 2 diabetes.

In a further aspect of the present disclosure, there is provided a pharmaceutical formulation as disclosed herein for use in the treatment and/or prevention of obesity.

In another aspect of the present disclosure, there is provided a pharmaceutical formulation as disclosed herein for use in the treatment and/or prevention of NAFLD.

In a further aspect of the present disclosure, there is provided a pharmaceutical formulation as disclosed herein for use in the treatment and/or prevention of NASH.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical formulation as disclosed herein in the manufacture of a medicament for treating type 2 diabetes.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutical formulation as disclosed herein in the manufacture of a medicament for treating obesity.

In another aspect of the present disclosure, there is provided a use of a pharmaceutical formulation as disclosed herein in the manufacture of a medicament for treating NAFLD.

In a further aspect of the present disclosure, there is provided a use of a pharmaceutical formulation as disclosed herein in the manufacture of a medicament for treating NASH.

DESCRIPTION

Accordingly, there is provided a pharmaceutical formulation comprising:

(i) a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

CLAIMS:

1. A pharmaceutical formulation comprising:

(i) a compound of the following formula

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Xaa28-Gly-Gly-Pro-Ser-Ser-Gly

wherein

Xaa2 is Aib;

Xaa28 is Glu or Ser;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with a C14-C24 fatty acid via a linker between the Lys at position 20 and the C14-C24 fatty acid, wherein the linker is ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)t, wherein t is 1 or 2; and

the C-terminal amino acid is optionally amidated (SEQ ID NO: 5);

(ii) a buffer;

(iii) a tonicity agent; and

(iii) an antioxidant,

wherein the pH of the formulation is 7.8 - 9.0.

2. The pharmaceutical formulation according to claim 1, wherein the compound is selected from the group consisting of:

(a) a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-Gly

wherein Xaa 2 is Aib;

Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)-CO-(CH2)18CO2H; and

the C-terminal amino acid is amidated (SEQ ID NO: 1);

(b) a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Ser-Gly-Gly-Pro-Ser-Ser-Gly

wherein Xaa 2 is Aib;
Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)2-CO-(CH2)18CO2H; and
the C-terminal amino acid is amidated (SEQ ID NO: 2);

(c) a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-Gly

wherein Xaa 2 is Aib;
Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)-CO-(CH2)16CO2H; and
the C-terminal amino acid is amidated (SEQ ID NO: 3);

(d) a compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Ser-Gly-Gly-Pro-Ser-Ser-Gly

wherein Xaa 2 is Aib;
Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)2-CO-(CH2)16CO2H; and
the C-terminal amino acid is amidated (SEQ ID NO: 4).

3. The pharmaceutical formulation according to claim 1 or claim 2, wherein the compound has the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-Gly

wherein Xaa 2 is Aib;
Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)-CO-(CH2)18CO2H; and
the C-terminal amino acid is amidated (SEQ ID NO: 1).

4. The pharmaceutical formulation according to any one of claims 1-3, wherein the formulation comprises 1 mg/mL to 100 mg/mL of the compound.

5. The pharmaceutical formulation according to any one of claims 1-4, wherein the buffer is selected from the group consisting of a phosphate buffer and a tris(hydroxymethyl)aminomethane (or 2-amino-2-hydroxymethyl-propane-1,3-diol[$(HOCH_2)_3CNH_2$]) buffer.

6. The pharmaceutical formulation according to any one of claims 1-5, wherein the formulation comprises 1mM to 20 mM of buffer.

7. The pharmaceutical formulation according to any one of claims 1-6, wherein the buffer is a tris(hydroxymethyl)aminomethane (Tris) buffer.

8. The pharmaceutical formulation according to claim 7, wherein the formulation comprises 10 mM Tris buffer.

9 The pharmaceutical formulation according to any one of claims 1-8, wherein the tonicity agent is selected from the group consisting of mannitol, sucrose, trehalose, propylene glycol, glycerin, sodium chloride and arginine hydrochloride.

10. The pharmaceutical formulation according to any one of claims 1-9,
wherein the formulation comprises 5 mg/mL to 150 mg/mL of the tonicity agent.

11. The pharmaceutical formulation according to any one of claims 1-10, wherein the tonicity agent is mannitol.

12. The pharmaceutical formulation according to claim 11, wherein the formulation comprises 45 - 55 mg/mL of mannitol.

13. The pharmaceutical formulation according to any one of claims 1-12, wherein the antioxidant is selected from the group consisting of radical scavengers, chelators or chain terminators.

14. The pharmaceutical formulation according to any one of claims 1-13, wherein the formulation comprises 0.05 - 10.0 mg/mL of the antioxidant.

15. The pharmaceutical formulation according to any one of claims 1-14, wherein the antioxidant is selected from the group consisting of EDTA, citric acid, ascorbic acid, butylated hydroxytoluene (BHT), butylated hydroxy anisole (BHA), sodium sulfite, p-amino benzoic acid, glutathione, propyl gallate, histidine, cysteine, methionine, ethanol and N-acetyl cysteine.

16. The pharmaceutical formulation according to claim 15, wherein the antioxidant is EDTA.

17. The pharmaceutical formulation according to claim 16, wherein the formulation comprises 0.2 – 1.0 mg/mL of EDTA.

18. The pharmaceutical formulation according to claim 16 or claim 17, wherein the formulation comprises 0.5 mg/mL of EDTA.

19. The pharmaceutical formulation according to claim 15, wherein the antioxidant is citric acid.

20. The pharmaceutical formulation according to claim 19, wherein the formulation comprises 5mM to 15mM citric acid.

21. The pharmaceutical formulation according to claim 18 or 19, wherein the formulation comprises 8mM to 12mM citric acid.

22. The pharmaceutical formulation according to any one of claims 19-21, wherein the formulation comprises 10mM citric acid.

23. The pharmaceutical formulation according to any one of claims 1-22, wherein the pH of the formulation is 8.0 – 8.6.

24. The pharmaceutical formulation according to any one of claims 1-23, wherein the pH of the formulation is 8.0 – 8.3.

25. The pharmaceutical formulation according to claim 1, comprising:

(i) 1 mg/mL to 100 mg/mL of the compound of the following formula:

His-Xaa2-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Glu-Lys-Lys-Ala-Lys-Glu-Phe-Val-Glu-Trp-Leu-Leu-Glu-Gly-Gly-Pro-Ser-Ser-Gly

wherein Xaa 2 is Aib;
Lys at position 20 is chemically modified by conjugation of the epsilon-amino group of the Lys side chain with ([2-(2-aminoethoxy)-ethoxy]-acetyl)2-(γ-Glu)-CO-(CH2)18CO2H; and
the C-terminal amino acid is amidated (SEQ ID NO: 1);

(ii) 10 mM of Tris buffer;

(iii) 46 mg/mL of mannitol;

(iv) 0.5 mg/mL of EDTA,

wherein the pH of the formulation is 8.0 – 8.3.

26. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of type 2 diabetes.

27. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of obesity.

28. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of NAFLD.

29. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of NASH.

30. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for treating type 2 diabetes.

31. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for treating obesity.

32. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for treating NAFLD.

33. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for treating NASH.