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

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

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

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

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

13. ~~A~~ 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. ~~A~~ 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. ~~A~~ 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. ~~A~~ The pharmaceutical formulation according to claim 15, wherein the antioxidant is EDTA.

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

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

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

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

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

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

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

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

25. ~~A~~ 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 method of treating and/or preventing type 2 diabetes, wherein the method comprises administering to a patient a therapeutically effective amount of a pharmaceutical formulation of any one of claims 1-25.~~

~~27. A method of treating and/or preventing obesity, wherein the method comprises administering to a patient a therapeutically effective amount of a pharmaceutical formulation of any one of claims 1-25.~~

~~28. A method of treating and/or preventing nonalcoholic fatty liver disease (NAFLD), wherein the method comprises administering to a patient a therapeutically effective amount of a pharmaceutical formulation of any one of claims 1-25.~~

~~29. A method of treating and/or preventing nonalcoholic steatohepatitis (NASH), wherein the method comprises administering to a patient a therapeutically effective amount of a pharmaceutical formulation of any one of claims 1-25.~~

~~30~~26. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of type 2 diabetes.

~~31~~27. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of obesity.

~~32~~28. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of NAFLD.

~~33~~29. A pharmaceutical formulation according to any one of claims 1-25 for use in the treatment and/or prevention of NASH.

~~34~~30. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for ~~use in the treatment of~~treating type 2 diabetes.

~~35~~31. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for ~~use in the treatment of~~treating obesity.

~~36~~32. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for ~~use in the treatment of~~treating NAFLD.

~~37~~33. Use of a pharmaceutical formulation according to any one of claims 1-25 in the manufacture of a medicament for ~~use in the treatment of~~treating NASH.