desirable control of peptide oligomerization.

Summary

In an aspect, there is provided a pharmaceutical composition comprising tirzepatide, or a pharmaceutically acceptable salt thereof; NaCl; glycerin; phenol; and phosphate buffer; wherein the NaCl concentration is less than or equal to about 3 mg/mL.

In another aspect, there is provided use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating type 2 diabetes in a human.

In another aspect, there is provided use of a pharmaceutical composition as described herein in the manufacture of a medicament for improving chronic weight management in a human in need thereof.

In another aspect, there is provided use of a pharmaceutical composition as described herein in the manufacture of a medicament for treating obesity.

In another aspect, there is provided a pharmaceutical composition as described herein for use in the treatment of type 2 diabetes.

In another aspect, there is provided a pharmaceutical composition as described herein for use to improve chronic weight management.

In another aspect, there is provided a pharmaceutical composition as described herein for use in treating obesity.

In another aspect, there is provided a pharmaceutical composition as described herein for use in therapy.

In another aspect, there is provided a pharmaceutical composition comprising SEQ ID NO:3, or a pharmaceutically acceptable salt thereof; NaCl; glycerin; phenol; and phosphate buffer; wherein the NaCl concentration is less than or equal to about 3 mg/mL.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1. Static light scattering of tirzepatide in solution containing 140 mM NaCl, pH 7.0.

FIG. 2. Static light scattering of tirzepatide in solution containing 140 mM NaCl and 5 mg/mL phenol, pH 7.0 and tirzepatide in solution containing 140 mM NaCl, pH 7.0.

FIG. 3. Static light scattering of tirzepatide in 200 mM NaCl; 140 mM NaCl; 85 mM NaCl; 30 mM NaCl; phenol with 0 mM NaCl; glycerin with 0 mM NaCl; and 0 mM NaCl.

FIG. 4. Static light scattering of tirzepatide in 30 mM NaCl and 8 mg/mL phenol; 30 mM

NaCl and 5 mg/mL phenol; 30 mM NaCl; 8 mg/mL phenol with 0 mM NaCl; and 5 mg/mL phenol with 0 mM NaCl.

FIG. 5. Static light scattering of tirzepatide in 30 mM NaCl with 15 mg/mL benzyl alcohol; 30 mM NaCl with 9 mg/mL benzyl alcohol; 30 mM NaCl; 15 mg/mL benzyl alcohol with 0 mM NaCl; and 9 mg/mL benzyl alcohol with 0 mM NaCl.

FIG. 6. Static light scattering of tirzepatide with 30 mM NaCl, 9 mg/mL benzyl alcohol, and 2 mg/mL phenol; 30 mM NaCl; and 9 mg/mL benzyl alcohol with 2 mg/mL phenol and 0 mM NaCl.

FIG. 7. Ligand-observed NMR of preservatives. In upper left is 1.8 mg/mL benzyl alcohol; upper right is 1.8 mg/mL benzyl alcohol plus 1 mg/mL tirzepatide; Lower left: 1.5 mg/mL phenol; Lower right: 1.5 mg/mL phenol plus 1.0 mg/mL tirzepatide.

FIG. 8. ^{1}H-^{13}C HSQC spectrum of tirzepatide (black) overlayed with that of tirzepatide with benzyl alcohol. No significant differences between the spectra are observed.

FIG. 9. ^{1}H-^{13}C HSQC spectrum of tirzepatide (black) overlayed with that of tirzepatide with phenol. Significant differences between the spectra are observed showing interaction of phenol with tirzepatide.

Applicants discovered that NaCl concentration is an important aspect involved in tirzepatide self-association.

In an embodiment is a preserved formulation wherein the oligomerization state of tirzepatide is considered equivalent, in accordance with United States regulatory standards, to the Mounjaro™ matrix. In an embodiment is a preserved tirzepatide formulation having a low risk of fibril formation.

WE CLAIM:

1. A pharmaceutical composition comprising tirzepatide, or a pharmaceutically acceptable salt thereof; NaCl; glycerin; phenol; and phosphate buffer; wherein the NaCl concentration is less than or equal to about 3 mg/mL.

2. A pharmaceutical composition as claimed by Claim 1, wherein the tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is:

(a) from about 2 to about 50 mg/mL;

(b) selected from the group consisting of about 5, about 10, about 15, about 20, about 25, about 30, about 40, and about 50 mg/mL;

(c) selected from the group consisting of about 10, about 20, and about 30 mg/mL;

(d) from about 4.2 to about 41.8 mg/mL;

(e) selected from the group consisting of about 4.17, about 8.33, about 12.5, about 16.67, about 20.83, about 25, about 33.33, and about 41.8 mg/mL; or

(f) selected from the group consisting of about 4.17, about 8.33, about 12.50, about 16.67, about 20.83, and about 25 mg/mL.

3. A pharmaceutical composition as claimed by claim 1 in a unit dose presentation, wherein the unit dose of tirzepatide, or pharmaceutically acceptable salt thereof, is selected from the group consisting of about 5, about 7.5, about 10, about 12.5, about 15, about 20, and about 25 mg.

4. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the dose volume to be administered is about 0.5 mL or about 0.6 mL.

5. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the phosphate buffer concentration is about 5 mM or about 1.34 mg/mL.

6. A pharmaceutical composition as claimed by any one of Claims 1 to 3 wherein the NaCl concentration is:

(a) from about 30 mM to about 50mM;

(b) about 30 mM; or

(c) about 1.75 mg/mL.

7. A pharmaceutical composition as claimed by any one of Claims 1 to 3, wherein the glycerin concentration is from about 8mg/mL to about 12 mg/mL or about 8 mg/mL.

8. A pharmaceutical composition as claimed by any one of Claims 1 to 3, wherein the phenol concentration is:

(a) from about 1.5 mg/mL to about 6 mg/mL;

(b) from about 2 mg/mL to about 5.5mg/mL; or

(c) about 5.5 mg/mL.

9. A pharmaceutical composition as claimed by any one of Claims 1 to 3, wherein the composition further comprises benzyl alcohol.

10. A pharmaceutical composition as claimed by Claim 9, wherein the composition further comprises about 9 mg/mL benzyl alcohol, low peroxide grade benzyl alcohol, and/or the benzyl alcohol has less than about 4 parts per million peroxide.

11. A pharmaceutical composition as claimed by any one of Claims 1 to 3, wherein the composition pH is from about 6.5 to about 7.5, from about 6.7 to about 7.3, or about 7.

12. A pharmaceutical composition as claimed by Claim 1 wherein tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is from about 5 to about 30 mg/mL; the phosphate buffer concentration is about 5mM; NaCl is about 2.93 mg/mL; Phenol is about 5.5mg/mL; and Glycerin is about 12mg/mL.

13. A pharmaceutical composition as claimed by Claim 1 wherein: tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is from about 5 to about 30 mg/mL; phosphate buffer concentration is about 5mM; NaCl is about 2.93 mg/mL; Phenol is about 2mg/mL; Glycerin is about 8mg/mL; and further comprising about 9 mg/mL benzyl alcohol.

14. A pharmaceutical composition as claimed by Claim 1 wherein tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is from about 4.17 mg/mL to about 25 mg/mL; Phosphate buffer concentration is about 5mM; NaCl concentration is about 30 mM; Glycerin; and Phenol.

15. A pharmaceutical composition as claimed by any one of Claims 1 to 14 wherein the composition is presented or to be administered in a multiuse injection device.

16. Use of a pharmaceutical composition as claimed by any one of Claims 1 to 15 in the manufacture of a medicament for treating type 2 diabetes in a human.

17. The use as claimed by Claim 16 wherein the dose is to be administered once weekly.

18. Use of a pharmaceutical composition as claimed by any one of Claims 1 to 15 in the manufacture of a medicament for improving chronic weight management in a human in

need thereof.

19. The use as claimed by Claim 18 wherein the human in need thereof is obese.

20. Use of a pharmaceutical composition as claimed by any one of Claims 1 to 15 in the manufacture of a medicament for treating obesity.

21. A pharmaceutical composition as claimed by any one of Claims 1 to 15 for use in the treatment of type 2 diabetes.

22. A pharmaceutical composition as claimed by any one of Claims 1 to 15 for use to improve chronic weight management.

23. A pharmaceutical composition as claimed by any one of Claims 1 to 15 for use in treating obesity.

24. A pharmaceutical composition as claimed by any one of Claims 1 to 15 for use in therapy.

25. A pharmaceutical composition comprising SEQ ID NO:3, or a pharmaceutically acceptable salt thereof; NaCl; glycerin; phenol; and phosphate buffer; wherein the NaCl concentration is less than or equal to about 3 mg/mL.