

assure safety (antimicrobial preservatives), minimise pain and irritation upon injection (tonicity agents), and control or prolong drug delivery (polymers). These are all examples of positive or synergistic interactions between excipients and medicinal products. However, any excipient added to the composition has the potential to produce negative effects such as loss of peptide solubility, activity, and/or chemical/physical stability, increased self-aggregation or fibrillation, which in turn may render the medicinal product unsafe for administration.

Thus, the formulation scientist has to investigate and optimise all components in a pharmaceutical composition, considering all interactions, including synergistic and antagonistic, between excipients and drugs in parenteral formulations. The present invention provides a surprisingly stable pharmaceutical composition comprising selected peptides.

The present invention concerns pharmaceutical compositions for parenteral administration of selected peptides disclosed in WO2018104561 (e.g. compound 18 of WO2018104561), which describes the compounds and their uses in detail. Example 4 of WO2018104561 provides test formulations of the compounds it discloses, however, it does not provide any parenteral pharmaceutical composition (e.g. none comprising a tonicity agent).

WO2016066818 discloses GLP-1 agonists, GLP-2 agonists and combinations thereof, and other GLP-1/GLP-2 dual agonists and formulations comprising PBS buffer containing 3% mannitol and 0.6% L-His, which may be suitable for parenteral administration of the disclosed GLP1/2-dual agonists.

WO2013164484 discloses GLP-2 analogues, and independently lists a series of tonicity agents (i.e. isotonicity makers) and suitable pH buffering agents as well as pH ranges considered suitable for these compounds.

None of these documents discloses the surprisingly stable pharmaceutical composition suitable for parenteral administration according to the present invention.

SUMMARY

This application describes chemically stable parenteral pharmaceutical compositions comprising one or more GLP-1/GLP-2 dual agonist. The application thus describes isotonic pharmaceutical compositions comprising one or more GLP-1/GLP-2 dual agonist comprising general formula A, suitable for parenteral administration to human subjects.

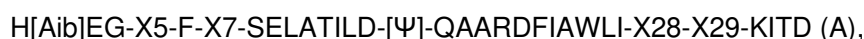
In one aspect, the present disclosure refers to an isotonic parenteral pharmaceutical composition,

comprising at least 1 mg/mL of one or more GLP-1/GLP-2 dual agonist comprising general formula A:

H[Aib]EG-X5-F-X7-SELATILD-[Ψ]-QAARDFIAWLI-X28-X29-KITD (A),

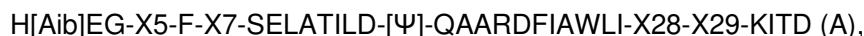
wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S; X29 is H and at least one of X5 and X7 is T, and wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and wherein said albumin binding moiety is K([17-carboxy-heptadecanoyl]-isoGlu), and wherein said composition further comprises 1-200 mM buffer component and 1-500 mM of a tonicity agent, preferably 50-450 mM of a tonicity agent, wherein said tonicity agent is an ionic tonicity agent selected from the group consisting of salts, alkali metals or earth metal halides, or a non-ionic tonicity agent which is mannitol, preferably D-mannitol, wherein said composition further comprises a solvent, and wherein said composition has a pH of pH 6.0 to pH 8.2, preferably a pH of pH 7.0 to pH 8.0.

In another aspect, the present disclosure refers to a method for improving the chemical stability of an isotonic parenteral pharmaceutical composition comprising: at least 1 mg/mL of one or more GLP-1/GLP-2 dual agonist comprising general formula A:



wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S; X29 is H and at least one of X5 and X7 is T, and wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)]; and phosphate buffer; wherein said method comprises adding mannitol, preferably D-mannitol, or a salt, preferably NaCl or KCl, to said composition.

In yet another aspect, the present disclosure refers to use of mannitol, preferably D-mannitol, or a salt, preferably NaCl or KCl, for improving the chemical stability of an isotonic parenteral pharmaceutical composition comprising: at least 1 mg/mL of one or more GLP-1/GLP-2 dual agonist comprising general formula A:



wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S; X29 is H and at least one of X5 and X7 is T, and wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)]; and phosphate buffer.

In some examples, particular and specific isotonic parenteral compositions are described in detail in the present disclosure and the numbered non-limiting examples comprised in said present disclosure.

The chemical stability at time point Y of GLP-1/GLP-2 dual agonist in any of the tested compositions disclosed herein can be expressed as the relative purity X^Y of the GLP-1/GLP-2 dual agonist and is determined by measuring the absolute purity X' of the GLP-1/GLP-2 dual agonist and normalising it to the absolute purity X^0 of the GLP-1/GLP-2 dual agonist at day zero (day 0), wherein said absolute purities are determined by HPLC at a given time point Y by identifying the purity of peak corresponding to the GLP-1/GLP-2 dual agonist.

It was surprisingly found, that the chemical stability of the disclosed GLP-1/GLP-2 dual agonists in parenteral pharmaceutical compositions, comprising mannitol as a non-ionic tonicity agent, have a stable and high chemical stability compared to pharmaceutical compositions comprising other tonicity agents, such as sucrose, dextrose, glycerol, propylene glycol, and mannitol when in combination with the buffer L-histidine.

It was surprisingly found, that the chemical stability of the disclosed GLP-1/GLP-2 dual agonists in parenteral pharmaceutical compositions comprising ionic tonicity agents, such as NaCl, have a chemical stability which is at least as good as (i.e. comparable to) pharmaceutical compositions not comprising any tonicity agent(s) and a higher normalised stability than compositions comprising other tonicity agents, such as sucrose, dextrose and glycerol.

CLAIMS

1. An isotonic parenteral pharmaceutical composition, comprising:
 - a. at least 1 mg/mL of one or more GLP-1/GLP-2 dual agonist comprising general formula A:

H[Aib]EG-X5-F-X7-SELATILD-[Ψ]-QAARDFIAWLI-X28-X29-KITD (A),

wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S; X29 is H and at least one of X5 and X7 is T, and
wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and
wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)]; and
 - b. 1 mM to 200 mM of buffer component; and
 - c. 1 mM to 500 mM of atonicity agent, preferably 50 mM to 450 mM of atonicity agent,wherein said tonicity agent is
 - (i) an ionic tonicity agent selected from the group consisting of salts, alkali metals or earth metal halides, or
 - (ii) a non-ionic tonicity agent which is mannitol, preferably D-mannitol,wherein said composition further comprises a solvent, and
wherein said composition has a pH of pH 6.0 to pH 8.2, preferably a pH of pH 7.0 to pH 8.0.
2. The isotonic parenteral pharmaceutical composition of claim 1 wherein
 - a. said non-ionic tonicity agent is D-mannitol; or
 - b. said ionic tonicity agent is selected from the group consisting of CaCl₂, KBr, KCl, LiCl, NaI, NaBr, NaCl or Na₂SO₄, preferably wherein the ionic tonicity agent is NaCl or KCl.
3. The parenteral pharmaceutical composition of any one of the preceding claims, wherein said one or more GLP-1/GLP-2 dual agonist comprising general formula A is of the general formula B:

H[Aib]EG-X5-FT-SELATILD-[Ψ]-QAARDFIAWLI-X28-HKITD (B),

wherein X5 is T or S; X28 is Q, E, A, H, Y, L, K, R or S and
wherein [Ψ] indicates an L or D lysine residue in which the albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist and
wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)],
preferably wherein said one or more GLP-1/GLP-2 dual agonist comprising general formula A or B comprises the sequence:

H[Aib]EGSFTSELATILD[Ψ]QAARDFIAWLIQHKITD (SEQ ID NO: 1),

preferably wherein said one or more GLP-1/GLP-2 dual agonist comprising general formula A or B is:

- a. Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (CPD1OH); or
- b. Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-NH₂ (CPD1NH₂).

4. The isotonic parenteral pharmaceutical composition according to any one of the preceding claims, wherein said buffer component is selected from the group consisting of phosphate buffer, citrate buffer, histidine buffer, tris buffer or bis tris, or a combination thereof, preferably selected from the group consisting of phosphate buffer, citrate buffer, tris buffer or bis tris, or a combination thereof, preferably wherein said buffer component is phosphate buffer, preferably wherein said buffer component is a sodium phosphate buffer, preferably wherein said sodium phosphate buffer is selected from disodium phosphate or sodium dihydrogen phosphate, or a combination thereof.

5. The isotonic parenteral pharmaceutical composition according to any preceding claim wherein said buffer component is at a final concentration of 15 mM to 200 mM, preferably 15mM to 30mM, preferably wherein said buffer component is at a final concentration of 20mM.

6. The isotonic parenteral pharmaceutical composition according to any one of claims 1 to 5 wherein, said mannitol is at a final concentration of 190 mM to 240 mM, preferably 230 mM.

7. The isotonic parenteral pharmaceutical composition according to any one of claims 1 to 5 wherein said tonicity agent is a salt, preferably NaCl or KCl, and wherein said salt is present at a final concentration of 50 mM to 450 mM, preferably 115 mM, most preferably the salt is NaCl at a final concentration of 115 mM.

8. The isotonic parenteral pharmaceutical composition of any one of the preceding claims, wherein the osmolality of the composition is 230 mOsmol/kg to 370 mOsmol/kg.

9. The isotonic parenteral pharmaceutical composition of any one of claims 1 to 6 or 8, wherein

- a. said buffer component is a phosphate buffer at a final concentration of 15 mM to 200 mM, preferably 20 mM, said tonicity agent is mannitol, preferably D-mannitol, at a final

concentration of 190 mM to 240 mM, preferably 230 mM, and said one or more GLP-1/GLP-2 dual agonist comprises SEQ ID NO: 1 or any pharmaceutically acceptable salt thereof, wherein the pH is between pH 7.0 and pH 8.0, preferably pH 8.0; or

b. said buffer component is a phosphate buffer at a final concentration of 15 mM to 30 mM, said tonicity agent is mannitol, preferably D-mannitol, at a final concentration of 230 mM and said one or more GLP-1/GLP-2 dual agonist comprises SEQ ID NO: 1 or any pharmaceutically acceptable salt thereof, wherein the pH is between pH 7.0 and pH 8.0, preferably pH 8.0.

10. The isotonic parenteral pharmaceutical composition of any one of claims 1 to 5, 7 or 8, wherein

a. said buffer component is a phosphate buffer at a final concentration of 15 mM to 200 mM, preferably 20 mM, said tonicity agent is a salt, preferably NaCl or KCl, at a final concentration of 50 mM to 450 mM, preferably 115 mM, and said one or more GLP-1/GLP-2 dual agonist comprises SEQ ID NO: 1 or any pharmaceutically acceptable salt thereof, wherein the pH is between pH 7.0 and pH 8.0, preferably pH 8.0; or

b. said buffer component is a phosphate buffer at a final concentration of 15 mM to 30 mM, wherein said tonicity agent is a salt, preferably NaCl or KCl, at a final concentration of 50 mM to 450 mM, preferably 115 mM, and said one or more GLP-1/GLP-2 dual agonist comprises SEQ ID NO: 1 or any pharmaceutically acceptable salt thereof.

11. The isotonic parenteral pharmaceutical composition of any one of the preceding claims, wherein said one or more GLP-1/GLP-2 dual agonist is present at a concentration of 1 mg/mL to 15 mg/mL.

12. The isotonic parenteral pharmaceutical composition of any one of claims 1 to 6, 8, 9 or 11, comprising

a. SEQ ID NO: 1 or a chloride salt thereof, a phosphate buffer at a concentration of 15 mM to 30 mM, preferably 20 mM, mannitol preferably D-mannitol at a concentration of 230 mM, water for injection and sodium hydroxide and/or hydrochloric acid for pH adjustment to a pH of pH 8.0, wherein said one or more GLP-1/GLP-2 dual agonist is CPD1OH or CPD1NH₂, preferably Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (CPD1OH) and is present at 2 mg/mL; or

b. SEQ ID NO: 1 or a chloride salt thereof, a phosphate buffer at a concentration of 15 mM to 30 mM, preferably 20 mM, mannitol preferably D-mannitol at a concentration of 230 mM, water for injection and sodium hydroxide and/or hydrochloric acid for pH adjustment to a pH of pH 8.0, wherein said one or more GLP-1/GLP-2 dual agonist is CPD1OH or CPD1NH₂,

preferably Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (CPD1OH) and is present at 10 mg/mL.

13. The isotonic parenteral pharmaceutical composition of any one of claims 1 to 5, 7, 8, 10 or 11, comprising

a. SEQ ID NO: 1 or a chloride salt thereof, a phosphate buffer at a concentration of 15 mM to 30 mM, preferably 20 mM, a salt, preferably NaCl or KCl, at a concentration of 115 mM, water for injection and sodium hydroxide and/or hydrochloric acid for pH adjustment to a pH of pH 8.0, wherein said one or more GLP-1/GLP-2 dual agonist is CPD1OH or CPD1NH₂, preferably Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (CPD1OH) and is present at 2 mg/mL; or

b. SEQ ID NO: 1 or a chloride salt thereof, a phosphate buffer at a concentration of 15 mM to 30 mM, preferably 20 mM, a salt, preferably NaCl or KCl, at a concentration of 115 mM, water for injection and sodium hydroxide and/or hydrochloric acid for pH adjustment to a pH of pH 8.0, wherein said one or more GLP-1/GLP-2 dual agonist is CPD1OH or CPD1NH₂, preferably Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (CPD1OH) and is present at 10 mg/mL.

14. The isotonic parenteral pharmaceutical composition of claim 12 or claim 13, wherein said one or more GLP-1/GLP-2 dual agonist is Hy-H[Aib]EGSFTSELATILD[K([17-carboxy-heptadecanoyl]-isoGlu)]QAARDFIAWLIQHKITD-OH (CPD1OH).

15. The isotonic parenteral pharmaceutical composition of any one of claims 1 to 6, 8, 9, 11, 12 or 14, wherein

a. said composition comprises the ingredients:

Component	Amount per mL (CPD1OH ₂)	Function
CPD1OH	2 mg	Drug Substance
Na ₂ HPO ₄ (anhydrous) Disodium phosphate, anhydrous / Dibasic sodium phosphate, anhydrous	2.65 mg	Buffer component
NaH ₂ PO ₄ (anhydrous) Sodium dihydrogen phosphate, anhydrous / Monobasic sodium phosphate, anhydrous	0.16 mg	Buffer component
Mannitol (D-mannitol)	41.90 mg	Tonicity agent
Hydrochloric acid	pH adjustment to pH 8	
Sodium Hydroxide	pH adjustment to pH 8	
Water for Injections	To make 1 mL	Solvent

; or

b. said composition comprises the ingredients:

Component	Amount per mL (CPD1OH ₂)	Function
CPD1OH	10 mg	Drug Substance
Na ₂ HPO ₄ (anhydrous) Disodium phosphate, anhydrous / Dibasic sodium phosphate, anhydrous	2.65 mg	Buffer component
NaH ₂ PO ₄ (anhydrous) Sodium dihydrogen phosphate, anhydrous / Monobasic sodium phosphate, anhydrous	0.16 mg	Buffer component
Mannitol (D-mannitol)	41.90 mg	Tonicity agent
Hydrochloric acid	pH adjustment to pH 8	
Sodium Hydroxide	pH adjustment to pH 8	
Water for Injections	To make 1 mL	Solvent

16. The isotonic parenteral pharmaceutical composition of any one of claims 1 to 5, 7, 8, 10, 11, 13 or 14, wherein

a. said composition comprises the ingredients:

Component	Amount per mL (CPD1OH ₂)	Function
CPD1OH	2 mg	Drug Substance
Na ₂ HPO ₄ (anhydrous) Disodium phosphate, anhydrous / Dibasic sodium phosphate, anhydrous	2.65 mg	Buffer component
NaH ₂ PO ₄ (anhydrous) Sodium dihydrogen phosphate, anhydrous / Monobasic sodium phosphate, anhydrous	0.16 mg	Buffer component
NaCl or KCl	6.7 mg NaCl or 8.6 mg KCl	Tonicity agent
Hydrochloric acid	pH adjustment to pH 8	
Sodium Hydroxide	pH adjustment to pH 8	
Water for Injections	To make 1 mL	Solvent

; or

b. said composition comprises the ingredients:

Component	Amount per mL (CPD1OH ₂)	Function
CPD1OH	10 mg	Drug Substance
Na ₂ HPO ₄ (anhydrous) Disodium phosphate, anhydrous / Dibasic sodium phosphate, anhydrous	2.65 mg	Buffer component
NaH ₂ PO ₄ (anhydrous) Sodium dihydrogen phosphate, anhydrous / Monobasic sodium phosphate, anhydrous	0.16 mg	Buffer component
NaCl or KCl	6.7 mg NaCl or 8.6 mg KCl	Tonicity agent
Hydrochloric acid	pH adjustment to pH 8	
Sodium Hydroxide	pH adjustment to pH 8	
Water for Injections	To make 1 mL	Solvent

17. The isotonic parenteral pharmaceutical composition of any one of the preceding claims, wherein said composition

- a. is suitable for *s.c.* or *i.v.* injection into human subjects; and/or
- b. has a shelf-life of at least 1, 2, 3, 4, 6, 12, 18 or 24 months, preferably at least 24 months; and/or
- c. has a chemical stability of at least 90% after 12 months storage; and/or
- d. has a chemical stability of at least 97% after 12 months storage, preferably storage at 5°C; and/or
- e. has a chemical stability of at least 97% after 24 months storage, preferably at 5°C.

18. A method for improving the chemical stability of an isotonic parenteral pharmaceutical composition comprising:

a. at least 1 mg/mL of one or more GLP-1/GLP-2 dual agonist comprising general formula A:

H[Aib]EG-X5-F-X7-SELATILD-[Ψ]-QAARDFIAWLI-X28-X29-KITD (A),

wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S; X29 is H and at least one of X5 and X7 is T, and

wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and

wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)]; and

b. phosphate buffer;

wherein said method comprises adding mannitol, preferably D-mannitol, or a salt, preferably NaCl or KCl, to said composition.

19. Use of mannitol, preferably D-mannitol, or a salt, preferably NaCl or KCl, for improving the chemical stability of an isotonic parenteral pharmaceutical composition comprising:

a. at least 1 mg/mL of one or more GLP-1/GLP-2 dual agonist comprising general formula A:

H[Aib]EG-X5-F-X7-SELATILD-[Ψ]-QAARDFIAWLI-X28-X29-KITD (A),

wherein X5 is T or S; X7 is T or S; X28 is Q, E, A, H, Y, L, K, R or S; X29 is H and at least one of X5 and X7 is T, and

wherein [Ψ] indicates an L or D lysine residue in which an albumin binding moiety is conjugated to the GLP-1/GLP-2 dual agonist, and

wherein said albumin binding moiety is [K([17-carboxy-heptadecanoyl]-isoGlu)]; and

b. phosphate buffer.

20. Use of the isotonic parenteral pharmaceutical composition of any one of the preceding claims, in the manufacture of a medicament for:

- (i) increasing intestinal mass, improving intestinal function, increasing intestinal blood flow, or repairing intestinal damage or dysfunction, in a subject in need thereof; or
- (ii) treating, or prophylaxis of malabsorption, ulcers, short-bowel syndrome, cul-de-sac syndrome, inflammatory bowel disease, irritable bowel syndrome, pouchitis, celiac sprue, tropical sprue, hypogammaglobulinemic sprue, mucositis induced by chemotherapy or radiation therapy, diarrhoea induced by chemotherapy or radiation therapy, low grade inflammation, metabolic endotoxemia, necrotising enterocolitis, primary biliary cirrhosis, hepatitis, fatty liver disease, or gastrointestinal side-effects of inflammatory conditions, in a subject in need thereof; or
- (iii) reducing or inhibiting weight gain, reducing gastric emptying or intestinal transit, reducing food intake, reducing appetite, or promoting weight loss, in a subject in need thereof; or
- (iv) treating or prophylaxis of obesity, morbid obesity, obesity-linked gallbladder disease, obesity-induced sleep apnoea, inadequate glucose control, glucose tolerance, dyslipidaemia, diabetes, pre-diabetes, metabolic syndrome or hypertension, in a subject in need thereof.