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(54) **PROPYLENE GLYCOL-CONTAINING PEPTIDE FORMULATIONS WHICH ARE OPTIMAL FOR PRODUCTION AND FOR USE IN INJECTION DEVICES**

FÜR DIE HERSTELLUNG UND VERWENDUNG IN INJEKTIONSVORRICHTUNGEN OPTIMALE PROPYLENGLYKOL ENHALTENDE PEPTIDFORMULIERUNGEN

FORMULATIONS PEPTIDIQUES A BASE DE PROPYLENE GLYCOL OPTIMALES POUR LA PRODUCTION ET L'UTILISATION DANS DES DISPOSITIFS D'INJECTION

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- **PRIDAL L ET AL: "ABSORPTION OF GLUCAGON-LIKE PEPTIDE-1 CAN BE PROTRACTED BY ZINC OR PROTAMINE", INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 136, 1 January 1996 (1996-01-01), pages 53-59, XP002938824, ISSN: 0378-5173, DOI: 10.1016/0378-5173(95)04480-9**

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to pharmaceutical formulations comprising the peptide Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) and propylene glycol.

BACKGROUND OF THE INVENTION

[0002] The inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known and one of the more common isotonic agents used in such formulations is mannitol. However, the present inventors have observed that mannitol causes problems during the production of peptide formulations as it crystallizes resulting in deposits in the production equipment and in the final product. Such deposits increase the need to clean the filling equipment during production of the formulation and this results in reduced production capability. In addition, such deposits may also result in reduced yield of the final product since vials/cartridges containing the peptide formulation may need to be discarded if particles are present. Finally, the present inventors have observed that in peptide formulations to be administered by injection, the presence of mannitol results in clogging of injection devices.

[0003] Accordingly, it is desirable to identify an alternative isotonic agent to mannitol for inclusion in peptide-containing formulations and in particular, for inclusion in peptide formulations which are administered by injection. PRIDAL L ET AL: "ABSORPTION OF GLUCAGON-LIKE PEPTIDE-1 CAN BE PROTRACTED BY ZINC OR PROTAMINE",INTERNATIONAL JOURNAL OF PHARMACEUTICS, ELSEVIER BV, NL, vol. 136, 1 January 1996 (1996-01-01), discloses a composition comprising GLP-1 (7-36) amide in combination with disodium phosphate and an isotonic agent glycerol at pH about 7 (pH= 6.9).

SUMMARY OF THE INVENTION

[0004] The present inventors have discovered that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices. The present compositions may be formulated with any peptide and are also physically and chemically stable thus rendering them shelf-stable and suitable for invasive (eg. injection, subcutaneous injection, intramuscular, intraveneous or infusion) as well as non-invasive (eg nasal, oral, pulmonary, transdermal or transmucosal e.g. buccal) means of administration.

[0005] The present invention therefore relates to a pharmaceutical formulation comprising the peptide Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) and propylene glycol, where the propylene glycol is present in a concentration of 1-100 mg/ml and the pH of the formulation is from 7-10. In a preferred embodiment, the pharmaceutical formulations of the invention further contain a buffer and a preservative.

The present invention is defined in the appended claims. Subject matters which are not encompassed by the scope of the claims do not form part of the present invention.

BRIEF DESCRIPTION OF THE FIGURES

[0006]

Figure 1 shows a photograph of dried droplets on microscope slides of from left to right, placebo (no peptide) formulations containing no isotonic agent (e only water, preservative and buffer), mannitol, sorbitol, xylitol, sucrose or glycerol as the isotonic agent with the far right slide containing mannitol with peptide Arg^{34}, Lys^{26}($N^{ε}$-(γ-Glu($N^{α}$-hexadecanoyl)))-GLP-1(7-37).

Figure 2 shows light microscopy pictures of from left to right, some of the dried droplets of placebo formulations containing mannitol, arginin, inositol or glycerol as the isotonic agent.

Figure 3 shows light microscopy pictures of clogged needles dosed with placebo formulations containing myoinositol, maltose or glycerol as the isotonic agent.

Figure 4 shows light microscopy pictures of deposits on needles dosed with placebo formulations containing glycine, lactose or mannitol as the isotonic agent.

Figure 5 shows filling equipment after 24 hours simulated filling with Arg^{34}, Lys^{26}($N^{ε}$-(γ-Glu($N^{α}$-hexadecanoyl)))-GLP-

1(7-37) medium containing myo-inositol.

Figure 6 shows deposits on filling equipment after 24 hours simulated filling with a mannitol-containing placebo formulation.

Figure 7 shows deposits on needles dosed with mannitol (top panel) and propylene glycol (bottom panel)-containing Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37) formulations.

DESCRIPTION OF THE INVENTION

[0007] The present invention relates to a pharmaceutical formulation comprising the peptide Arg^{34}, Lys^{26}(N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37) and propylene glycol where the final concentration of propylene glycol in the formulation is 1-100 mg/ml and the pH of the formulation is in the range of from 7-10.

[0008] The pharmaceutical formulations of the invention are found to be optimal for production because they exhibit reduced deposits in production equipment relative to formulations containing other isotonicity agents as measured by the simulated filling studies described in the Examples. In addition, the pharmaceutical formulations of the invention are found to be optimal for use in injection devices because they exhibit reduced clogging of the injection devices relative to formulations containing other isotonicity agents as measured by the simulated in use studies described in the Examples.

[0009] The peptide to be included in the formulation of the invention is a GLP-1 agonist as defined in the present claims where "a GLP-1 agonist" is understood to refer to a peptide which fully or partially activates the human GLP-1 receptor. In a preferred embodiment, the "GLP-1 agonist" is a peptide as defined in the present claims that binds to a GLP-1 receptor, preferably with an affinity constant (K_D) or a potency (EC_{50}) of below 1 μM, e.g. below 100 nM as measured by methods known in the art (see e.g. WO 98/08871) and exhibits insulinotropic activity, where insulinotropic activity may be measured in vivo or in vitro assays known to those of ordinary skill in the art. For example, the GLP-1 agonist may be administered to an animal and the insulin concentration measured over time.

[0010] The GLP-1 agonist is Arg^{34}, $Lys^{26}(N^{\varepsilon}$-(γ-Glu(N^{α}-hexadecanoyl)))-GLP-1(7-37).

[0011] The GLP-1 agonist is present in a concentration from 0.1 mg/ml to 100 mg/ml, more preferably in a concentration from 0.1 mg/ml to 50 mg/ml, and most preferably in a concentration of from 0.1 mg/ml to 10 mg/ml.

[0012] In one embodiment, the final concentration of propylene glycol in the formulations of the invention is from 1 to 50 mg/ml.

[0013] In another embodiment, the final concentration of propylene glycol in the formulations of the invention is from 5 to 25 mg/ml.

[0014] In yet another embodiment, the final concentration of propylene glycol in the formulations of the invention is from 8 to 16 mg/ml.

[0015] In yet a further embodiment, the final concentration of propylene glycol in the formulations of the invention is from 13 to 15 mg/ml.

[0016] In still another embodiment, the final concentration of propylene glycol in the formulations of the invention is from 13.5 to 14.5 mg/ml.

[0017] In another embodiment of the invention, the formulation has a pH in the range from 7.0 to 9.5.

[0018] In a further embodiment of the invention, the formulation has a pH in the range from 7.0 to 8.0.

[0019] In yet a further embodiment of the invention, the formulation has a pH in the range from 7.2 to 8.0.

[0020] In a further embodiment of the invention, the formulation has a pH in the range from 7.0 to 8.3.

[0021] In yet a further embodiment of the invention, the formulation has a pH in the range from 7.3 to 8.3.

[0022] In a preferred embodiment of the invention, the formulations contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

[0023] Where a buffer is to be included in the formulations of the invention, the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, or mixtures thereof. Each one of these specific buffers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the buffer is glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures thereof.

[0024] Where a pharmaceutically acceptable preservative is to be included in the formulations of the invention, the preservative is selected from the group consisting of phenol, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures thereof. Each one of these specific preservatives constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the preservative is phenol or m-cresol.

[0025] In a further embodiment of the invention the preservative is present in a concentration from 0.1 mg/ml to 50 mg/ml, more preferably in a concentration from 0.1 mg/ml to 25 mg/ml, and most preferably in a concentration from 0.1

mg/ml to 10 mg/ml.

[0026] The use of a preservative in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0027] In a further embodiment of the invention the formulation may further comprise a chelating agent where the chelating agent may be selected from salts of ethlenediaminetetraacetic acid (EDTA), citric acid, and aspartic acid, and mixtures thereof. Each one of these specific chelating agents constitutes an alternative embodiment of the invention.

[0028] In a further embodiment of the invention the chelating agent is present in a concentration from 0.1 mg/ml to 5mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 0.1mg/ml to 2mg/ml. In a further embodiment of the invention the chelating agent is present in a concentration from 2mg/ml to 5mg/ml.

[0029] The use of a chelating agent in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0030] In a further embodiment of the invention the formulation may further comprise a stabiliser selected from the group of high molecular weight polymers or low molecular compounds where such stabilizers include polyethylene glycol (e.g. PEG 3350), polyvinylalcohol (PVA), polyvinylpyrrolidone, carboxymethylcellulose, different salts (e.g. sodium chloride), L-glycine, L-histidine, imidazole, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and mixtures thereof. Each one of these specific stabilizers constitutes an alternative embodiment of the invention. In a preferred embodiment of the invention the stabiliser is selected from the group consisting of L-histidine, imidazole and arginine.

[0031] In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1mg/ml to 50mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 5mg/ml to 10mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 0mg/ml to 20mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 20mg/ml to 30mg/ml. In a further embodiment of the invention the high molecular weight polymer is present in a concentration from 30mg/ml to 50mg/ml.

[0032] In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1mg/ml to 50mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 0.1mg/ml to 5mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 5mg/ml to 10mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 10mg/ml to 20mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 20mg/ml to 30mg/ml. In a further embodiment of the invention the low molecular weight compound is present in a concentration from 30mg/ml to 50mg/ml.

[0033] The use of a stabilizer in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0034] In a further embodiment of the invention the formulation of the invention may further comprise a surfactant where a surfactant may be selected from a detergent, ethoxylated castor oil, polyglycolyzed glycerides, acetylated monoglycerides, sorbitan fatty acid esters, poloxamers, such as 188 and 407, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene derivatives such as alkylated and alkoxylated derivatives (tweens, e.g. Tween-20, or Tween-80), monoglycerides or ethoxylated derivatives thereof, diglycerides or polyoxyethylene derivatives thereof, glycerol, cholic acid or derivatives thereof, lecithins, alcohols and phospholipids, glycerophospholipids (lecithins, kephalins, phosphatidyl serine), glyceroglycolipids (galactopyransoide), sphingophospholipids (sphingomyelin), and sphingoglycolipids (ceramides, gangliosides), DSS (docusate sodium, docusate calcium, docusate potassium, SDS (sodium dodecyl sulfate or sodium lauryl sulfate), dipalmitoyl phosphatidic acid, sodium caprylate, bile acids and salts thereof and glycine or taurine conjugates, ursodeoxycholic acid, sodium cholate, sodium deoxycholate, sodium taurocholate, sodium glycocholate, N-Hexadecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate, anionic (alkyl-aryl-sulphonates) monovalent surfactants, palmitoyl lysophosphatidyl-L-serine, lysophospholipids (e.g. 1-acyl-sn-glycero-3-phosphate esters of ethanolamine, choline, serine or threonine), alkyl, alkoxyl (alkyl ester), alkoxy (alkyl ether)-derivatives of lysophosphatidyl and phosphatidylcholines, e.g. lauroyl and myristoyl derivatives of lysophosphatidylcholine, dipalmitoylphosphatidylcholine, and modifications of the polar head group, that is cholines, ethanolamines, phosphatidic acid, serines, threonines, glycerol, inositol, and the postively charged DODAC, DOTMA, DCP, BISHOP, lysophosphatidylserine and lysophosphatidylthreonine, zwitterionic surfactants (e.g. N-alkyl-N,N-dimethylammonio-1-propanesulfonates, 3-cholamido-1-propyldimethylammonio-1-propanesulfonate, dodecylphosphocholine, myristoyl lysophosphatidylcholine, hen egg lysolecithin), cationic surfactants (quarternary ammonium bases) (e.g. cetyltrimethylammonium bromide, cetylpyridinium chloride), non-ionic surfactants, polyethyleneoxide/polypropyleneoxide block copolymers (Pluronics/Tetronics, Triton X-100, Dodecyl β-D-glucopyranoside) or polymeric surfactants (Tween-40, Tween-80, Brij-35), fusidic acid derivatives- (e.g. sodium tauro-dihydrofusidate etc.), long-chain fatty acids and salts thereof C6-C12 (eg. oleic acid and caprylic acid), acylcarnitines and derivatives, N^{α}-acylated derivatives of lysine, arginine or histidine, or side-chain acylated derivatives of lysine or arginine, N^{α}-acylated derivatives of dipeptides comprising any combination of lysine, arginine or histidine and a neutral or acidic amino acid, N^{α}-acylated derivative of a tripeptide comprising any combination of a neutral amino acid and two

charged amino acids, or the surfactant may be selected from the group of imidazoline derivatives, or mixtures thereof. Each one of these specific surfactants constitutes an alternative embodiment of the invention.

[0035] The use of a surfactant in pharmaceutical compositions is well-known to the skilled person. For convenience reference is made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

[0036] The formulations of the invention may be prepared by conventional techniques, e.g. as described in Remington's Pharmaceutical Sciences, 1985 or in Remington: The Science and Practice of Pharmacy, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product..

[0037] As mentioned above, in a preferred embodiment, the formulations of the invention-contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative.

[0038] As the formulations of the invention are optimal for production and for use in injection devices since they exhibit reduced deposits of production equipment and reduced clogging of injection devices, the above methods of production can be used to produce peptide formulations suitable for use in production and/or for use in injection devices.

[0039] The formulations of the invention are suitable for administration to a mammal, preferably a human. The route of administration of the formulations of the invention may be any route which effectively transports the peptide contained in the formulation to the appropriate or desired site of action, such as oral, nasal, buccal, pulmonal, transdermal or parenteral.

[0040] Due to the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular, in a preferred embodiment, the formulations of the invention are to be administered parenterally to a patient in need thereof. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump.

[0041] A further option is a composition which may be a powder or a liquid for the administration of the formulation in the form of a nasal or pulmonal spray. As a still further option, the formulation can also be administered transdermally, e.g. from a patch, optionally a iontophoretic patch, or transmucosally, e.g. bucally. The above-mentioned possible ways to administer the formulations of the invention are not to be considered as limiting the scope of the invention.

[0042] The following examples illustrate various aspects of the invention but are in no way intended to limit the scope thereof.

EXAMPLES

EXAMPLE 1

Simulated filling experiments, drop and clogging tests of replacement candidates for mannitol

[0043] As laboratory experiments have shown that with regards to clogging of needles and deposits on needles, formulations without peptide ("placebo") give the same conclusions as formulations with peptide at 0.3-5.0 mg/ml, the screening studies in Example 1 have been done using placebo except where indicated otherwise.

Preparation of Formulations With Different Isotonic Agents

[0044] Preservative (5.5 mg/ml phenol) and buffer 1.24 mg/ml disodium hydrogen phosphate, dihydrate) were dissolved in water and the isotonic agent was added while stirring. pH was adjusted to pH 7.9 using Sodium Hydroxide and/or Hydrochloric acid. Finally, the formulation was filtered through a 0.22 μm filter. The isotonic agents tested in each formulation and their concntrations are shown in Table 1.

Table 1 Composition of the tested formulations

Formulation no.	Tonicity modifier
1	Glucose monohydrate (38.0 mg/ml)
2	Laktose monohydrate (65.0 mg/ml)
3	Maltose (67.2 mg/ml)
4	Glycine (15.1 mg/ml)
5	Polyethylenglycol 400 (77.5 mg/ml)
6	L-arginin (24.6 mg/ml)

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