US008846618B2

(12) **United States Patent**
Flink et al.

(10) **Patent No.: US 8,846,618 B2**
(45) **Date of Patent: Sep. 30, 2014**

(54) **STABLE FORMULATION OF MODIFIED GLP-1**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **12/785,861**

(22) Filed: **May 24, 2010**

(65) **Prior Publication Data**

US 2010/0234299 A1 Sep. 16, 2010

Related U.S. Application Data

(63) Continuation of application No. 11/786,095, filed on Apr. 11, 2007, now abandoned, which is a continuation of application No. 10/185,923, filed on Jun. 27, 2002, now abandoned.

(60) Provisional application No. 60/308,325, filed on Jul. 27, 2001, provisional application No. 60/308,297, filed on Jul. 27, 2001.

(30) **Foreign Application Priority Data**

Jun. 28, 2001	(DK)	2001 01010
Jun. 28, 2001	(DK)	2001 01011
Jul. 4, 2001	(DK)	2001 01052
Jul. 4, 2001	(DK)	2001 01053
Jan. 18, 2002	(DK)	2002 00093

(51) **Int. Cl.**

A61K 38/26	(2006.01)
A61P 3/10	(2006.01)
A61P 7/12	(2006.01)
C07K 14/605	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 14/605*** (2013.01); ***A61K 38/26*** (2013.01)

USPC **514/11.7**

(58) **Field of Classification Search**

CPC A61K 38/26; C07K 14/605

See application file for complete search history.

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(57) **ABSTRACT**

Pharmaceutical formulations of GLP-1 compounds and methods for preparation thereof.

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STABLE FORMULATION OF MODIFIED GLP-1

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. application Ser. No. 11/786,095 filed on Apr. 11, 2007, which is a continuation of U.S. application Ser. No. 10/185,923 filed on Jun. 27, 2002 and claims priority under 35 U.S.C. 119 of Danish Application No. PA 2001 01010 filed Jun. 28, 2001; Danish Application No. PA 2001 01011 filed Jun. 28, 2001; Danish Application No. PA 2001 01052 filed Jul. 4, 2001; Danish Application No. PA 2001 01053 filed Jul. 4, 2001; and Danish Application No. PA 2002 00093 filed Jan. 18, 2002; and U.S. Provisional Applications No. 60/308,325 filed Jul. 27, 2001 and 60/308,297 filed Jul. 27, 2001, the contents of which are fully incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulations comprising GLP-1 compounds, uses thereof and methods for preparing said formulations.

BACKGROUND OF THE INVENTION

Peptides are widely used in medical practice, and since they can be produced by recombinant DNA technology it can be expected that their importance will increase also in the years to come.

The hormones regulating insulin secretion belong to the so-called enteroinsular axis, designating a group of hormones, released from the gastrointestinal mucosa in response to the presence and absorption of nutrients in the gut, which promote an early and potentiated release of insulin. The enhancing effect on insulin secretion, the so-called incretin effect, is probably essential for a normal glucose tolerance. Many of the gastrointestinal hormones, including gastrin and secretin (cholecystokinin is not insulinotropic in man), are insulinotropic, but the only physiologically important ones, those that are responsible for the incretin effect, are the glucose-dependent insulinotropic polypeptide, GIP, and glucagon-like peptide-1 (GLP-1). Because of its insulinotropic effect, GIP, isolated in 1973 immediately attracted considerable interest among diabetologists. However, numerous investigations carried out during the following years clearly indicated that a defective secretion of GIP was not involved in the pathogenesis of insulin dependent diabetes mellitus (IDDM) or non insulin-dependent diabetes mellitus (NIDDM). Furthermore, as an insulinotropic hormone, GIP was found to be almost ineffective in NIDDM. The other incretin hormone, GLP-1 is the most potent insulinotropic substance known. Unlike GIP, it is surprisingly effective in stimulating insulin secretion in NIDDM patients. In addition, and in contrast to the other insulinotropic hormones (perhaps with the exception of secretin) it also potently inhibits glucagon secretion. Because of these actions it has pronounced blood glucose lowering effects particularly in patients with NIDDM.

GLP-1, a product of the proglucagon, is one of the youngest members of the secretin-VIP family of peptides, but is already established as an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism. The glucagon gene is processed

tion of 1) glucagon itself, occupying positions 33-61 of proglucagon (PG); 2) an N-terminal peptide of 30 amino acids (PG (1-30)) often called glicentin-related pancreatic peptide, GRPP; 3) a hexapeptide corresponding to PG (64-69); 4) and, finally, the so-called major proglucagon fragment (PG (72-158)), in which the two glucagon-like sequences are buried. Glucagon seems to be the only biologically active product. In contrast, in the intestinal mucosa, it is glucagon that is buried in a larger molecule, while the two glucagon-like peptides are formed separately.

While much attention has been focused on the pharmacological properties of acylated GLP-1 compounds, hitherto little is known about their physico-chemical and solution structural properties. Such knowledge is a prerequisite for rational handling during e.g. production, purification and formulation work and is eventually important for understanding of the structural basis for the protraction mechanism.

It is an important technical challenge to ensure prolonged stability during storage (shelf life) of many protein based drug products due to the inherent lability of macromolecules. Hence, proteins are sensitive to both chemical and physical degradation unlike many small molecules. Chemical degradation involves covalent bonds, such as hydrolysis, racemization, oxidation or crosslinking. Physical degradation involves conformational changes relative to the native structure, which includes loss of higher order structure, aggregation, precipitation or adsorption to surfaces. GLP-1 is known to be prone to instability due to aggregation. Both degradation pathways may ultimately lead to loss of biological activity of the protein drug.

GLP-1 and analogues of GLP-1 and fragments thereof are potentially useful i.a. in the treatment of type 1 and type 2 diabetes. However, solubility limitations and the low stability against the actions of endogenous diaminopeptidyl peptidase limits the usefulness of these compounds, and thus there still is a need for improvements in this field.

In WO 99/43341 are disclosed certain pharmaceutical formulations comprising GLP-1 having a lipophilic substituent. All of the disclosed formulations are maintained at pH 7.4.

In WO 00/37098 are disclosed shelf-stable formulations comprising GLP-1, a preservative, and a tonicity modifier, at pH 8.2 to 8.8.

Human GLP-1 is a 37 amino acid residue peptide originating from preproglucagon which is synthesised i.a. in the L-cells in the distal ileum, in the pancreas and in the brain. Processing of preproglucagon to give GLP-1(7-36)amide, GLP-1(7-37) and GLP-2 occurs mainly in the L-cells. A simple system is used to describe fragments and analogues of this peptide. Thus, for example, Val^8-GLP-1(7-37) (or Val8GLP-1(7-37)) designates a fragment of GLP-1 formally derived from GLP-1 by deleting the amino acid residues Nos. 1 to 6 and substituting the naturally occurring amino acid residue in position 8 (Ala) by Val. Similarly, $Lys^{34}(N^{\epsilon}$-tetradecanoyl)-GLP-1(7-37) designates GLP-1(7-37) wherein the ϵ-amino group of the Lys residue in position 34 has been tetradecanoylated. For convenience the amino acid sequence of GLP-1 (7-37) is given below, wherein the N-terminal His is no. 7 and the C-terminal Gly is no. 37:

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                                    (SEQ ID NO.: 1)
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-

Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-
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Where reference in this text is made to C-terminally extended GLP-1 analogues, the amino acid residue in position 38 is Arg unless otherwise indicated, the optional amino acid residue in position 39 is also Arg unless otherwise indicated and the optional amino acid residue in position 40 is Asp unless otherwise indicated. Also, if a C-terminally extended analogue extends to position 41, 42, 43, 44 or 45, the amino acid sequence of this extension is as in the corresponding sequence in human preproglucagon unless otherwise indicated.

SUMMARY OF THE INVENTION

We have discovered that certain modified GLP-1 or analogues thereof when formulated in aqueous solution together with a buffer, are physically stable at high concentrations of the modified GLP-1 or analogues thereof, when kept in the pH range from about 7 to about 10. The present formulations are physically stable within a given shelf life period at the recommended storage temperature (typically 2-3 years at 2-8° C.). Furthermore, the present formulations are physically stable during in-use (typically 1 month at accelerated temperatures e.g. 25° C. or 37° C.). The formulations of the invention are also chemically stable thus rendering them shelf-stable and suitable for invasive (eg. injection, subcutaneous injection, intramuscular, intravenous or infusion) as well as non-invasive (eg nasal or pulmonary, transdermal or transmucosal e.g. buccal) means of administration. When the inventive formulation comprising a GLP-1 compound was compared to the same formulation comprising GLP-1(7-37) substituted for the GLP-1 compound, the physical stability was increased considerably, and typically the shelf-life was increased from a few seconds to several months in the tests used.

One object of the present invention is to provide a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10;

Another object of the present invention is to provide a method of preparing a physically stable pharmaceutical formulation of a GLP-1 compound wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, comprising preparing a formulation containing the GLP-1 compound, and a buffer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10.

In one aspect of the invention the formulation contains a GLP-1 compound in a concentration from 1 mg/ml to 100 mg/ml.

In another aspect of the invention the formulation has a pH from 7.5 to 10.

In one embodiment the GLP-1 compound is Arg^{34}, Lys^{26} (N-ε-(γ-Glu(N-α-hexadecanoyl)))-GLP-1(7-37).

DESCRIPTION OF THE INVENTION

In one aspect the invention relates to a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10;

provided that if an isotonic agent is present and pH is 7.4 then mannitol or NaCl is not the isotonic agent.

In another aspect the invention relates to a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10;

provided that if an isotonic agent is present and pH is 7.4 then mannitol or NaCl is not the isotonic agent.

In a further aspect the invention relates to a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml or above, and wherein said formulation has a pH from 7.0 to 10.

In a further aspect the invention relates to a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 1 mg/ml or above, and wherein said formulation has a pH from 7.0 to 10.

In a further aspect the invention relates to a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof, wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10.

In a further aspect the invention relates to a pharmaceutical formulation comprising a GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1(7-37) or an analogue thereof, wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10.

In a further aspect the invention relates to a method of preparing a physically stable pharmaceutical formulation of a GLP-1 compound wherein said GLP-1 compound is GLP-1 (7-37) or an analogue thereof, wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, comprising preparing a formulation containing the GLP-1 compound, and a buffer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml or above, and wherein said formulation has a pH from 7.0 to 10.

In a further aspect the invention relates to a method of preparing a physically stable pharmaceutical formulation of a GLP-1 compound wherein said GLP-1 compound is GLP-1 (7-37) or an analogue thereof, wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, comprising preparing a formulation containing the GLP-1 compound, and a buffer, wherein said GLP-1 compound is present in a concentration from 1 mg/ml

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