(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 September 2016 (01.09.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/138436 A2

(51) International Patent Classification:
A61K 38/35 (2006.01)

(21) International Application Number:
PCT/US20 16/0 19873

(22) International Filing Date:
26 February 2016 (26.02.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/121,249 26 February 2015 (26.02.2015) US

(71) Applicant: **RETROPHIN, INC.** [US/US]; 12255 El Camino Real, Suite 250, San Diego, California 92130 (US).

(72) Inventors: **MACIKENAS, Dainius;** 30 IB HiUcrest Drive, Encinitas, California 92024 (US). **RUBY, Kale;** 1030 Saxony Road, Encinitas, California 92024 (US). **KOROBETSKAYA, Elena;** 3936 Iowa Street, San Diego, California 92104 (US).

(74) Agents: **SARGEANT, Brooke** et al; Seed Intellectual Property Law Group PLLC, Suite 5400, 701 Fifth Avenue, Seattle, Washington 98104-7064 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK,

[Continued on next page]

(54) Title: ADRENOCORTICOTROPIC HORMONE ANALOGUE FORMULATIONS

(57) Abstract: Formulations for administration of tetracosactide are provided. Methods of using such formulations for the treatment of various disorders, such as ACTH deficiency, infantile spasms, and multiple sclerosis, are also provided.

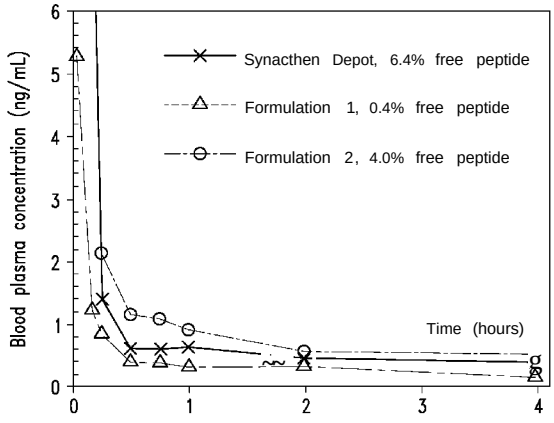

FIG. 6B

WO 2016/138436 A2

SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Hi))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

— *with sequence listing part of description (Rule 5.2(a))*

ADRENOCORTICOTROPIC HORMONE ANALOGUE FORMULATIONS

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification. The name of the text file containing the Sequence Listing is 790116_413WO_SEQUENCE_LISTING. The text file is 1.1 KB, was created on February 21, 2016, and is being submitted electronically viaEFS-Web.

BACKGROUND

Technical Field

The present invention relates to pharmaceutical formulations for administration of tetracosactide, and their use in the treatment of a wide variety of diseases and disorders.

Description of the Related Art

Adrenocorticotropic hormone (ACTH), also known as corticotropin, is a hormone synthesized by the pituitary gland. Human ACTH peptide is thirty-nine amino acids in length, having the amino acid sequence:

H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-T rp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-Asp-Gly-Ala-Glu-Asp-Gln-Leu-Ala-Glu-Ala-Phe-Pro-Leu-Glu-Phe-OH (SEQ. ID. NO.: 1).

Synthetic forms of ACTH have been identified that have biological effects similar to natural ACTH but have the advantage of being fully synthetic. For example, tetracosactide (or cosyntropin) is a synthetic analogue of ACTH that comprises the first twenty-four amino acids of ACTH.

In some pharmaceutical formulations for administering such ACTH synthetic analogues, the peptide exists freely in aqueous solution at an amount higher than is needed to achieve a therapeutic effect. It would be advantageous to develop formulations wherein the free peptide in the solution does not exceed the amount necessary to achieve a therapeutic effect, reducing or preventing a spike in plasma concentration of the synthetic ACTH peptide following administration and possibly providing longer duration of action.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a diffractogram showing the X-ray powder diffraction pattern (XRPD) of the solid phase of Formulation 1 (Example 1), indicating that the solid phase is amorphous material.

FIG. 2 is a diagram of the vessel assembly used in Example 2.

FIG. 3 shows diffractogram showing the X-ray powder diffraction pattern (XRPD) of the solid phase of Formulation 2 (Example 2), indicating that the solid phase is amorphous material.

FIG. 4 shows a diffractogram showing the X-ray powder diffraction partem (XRPD) of the solid phase of Formulation 3 (Example 3), indicating that the solid phase is amorphous material.

FIG. 5 is a graph illustrating the relationship between peptide solution addition rate and the percentage of free peptide in solution (as a percentage of total peptide). Several tetracosactide formulations were prepared using the methods described herein *(see* Table 1). The addition rate of the peptide-zinc solution to the second solution was varied to produce different formulations. The percentage of peptide free in solution was lower when faster addition rates were used.

FIG. 6 is a graph illustrating mean blood plasma levels of tetracosactide in rats over time, post-intramuscular administration of tetracosactide formulations («=12 total; *n=4* per formulation), showing all data points (a), and showing a subset of the data in greater detail wherein the y-axis has been truncated to a lower maximum value to improve visual display (b).

BRIEF SUMMARY

Embodiments of the present invention relate to pharmaceutical formulations for administering tetracosactide, and their use in treating a wide variety of diseases or disorders. Some of the embodiments have concentrations of free tetracosactide peptide in solution below about 5%. Without wishing to be bound by any particular theory, it is believed that the rate of addition of a metal salt solution to a counterion salt solution during preparation of the formulation influences properties of the precipitate and the adsorbtion of the peptide onto it. Because tetracosactide exists freely in the aqueous solutions of the formulations at a low concentration, upon administration to a subject, the formulations of the present invention may exhibit a lower **Cmax** than comparable formulations having a higher percent of free peptide in solution.

Accordingly, in one embodiment a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, is provided.

Some other embodiments provide a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, and the concentration of tetracosactide is from 0.1 mg/mL to 2 mg/mL, from 0.1 mg/mL to 1 mg/mL, or 1 mg/mL.

In still other embodiments, the invention comprises a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4%, less than or equal to 3%, less than or equal to 2%, less than or equal to 1%, less than or equal to 0.5%, or less than or equal to 0.1% of said tetracosactide is present as free peptide in solution.

In still other embodiments, the invention comprises a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, and said insoluble metal-based peptide complexing agent comprises zinc or aluminum.

In still other embodiments, the invention comprises a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, and said insoluble metal-based peptide complexing agent comprises a zinc salt.

In still other embodiments, the invention comprises a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, the insoluble metal-based peptide complexing agent is a zinc phosphate salt, and the concentration of zinc is from 0.5 mg/mL to 10 mg/mL, from 1 mg/mL to 5 mg/mL, from 2 mg/mL to 3 mg/mL, or 2.5 mg/mL.

Other embodiments provide a method for treating a subject having a disease amenable to treatment with a pan melanocortin receptor antagonist, comprising administering to a subject in need thereof a pharmaceutical formulation described

herein. Some embodiments of the invention provide a method for treating a disease for which the standard of care involves steroid therapy, comprising administering to a subject in need thereof a pharmaceutical formulation described herein. In some embodiments, the invention comprises a method for treating infantile spasms (West Syndrome), Idiopathic Membranous Nephropathy, Minimal change disease, deuchenne muscular dystrophy, multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic dermatomyositis, severe erythema multiforme, Stevens-Johnson syndrome, serum sickness, keratitis, iritis, iridocyclitis, diffuse posterior uveitis, choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation, or symptomatic sarcoidosis, comprising administering to a subject in need thereof a pharmaceutical formulation described herein.

These and other aspects of the invention will be apparent upon reference to the following detailed description.

DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention. However, one skilled in the art will understand that the invention may be practiced without these details.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

As used herein, certain items may have the following defined meanings.

Unless the context requires otherwise, throughout the present specification and claims, the transitional word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to." "Consisting of shall mean excluding more than trace elements of other ingredients and substantial method steps for administering the composition of this invention. Embodiments defined by each of the transitional terms are within the scope of this invention.

Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all

referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

As used in the specification and claims, the singular form "a", "an" and "the" include plural references unless the context clearly dictates otherwise. For example, the term "a cell" includes a plurality of cells, including mixtures thereof. Similarly, use of "a compound" for treatment or for the preparation pharmaceutical compositions contemplates using one or more compounds for such treatment or preparation unless the context clearly dictates otherwise.

As used herein, "about" and "approximately" generally refer to an acceptable degree of error for the quantity measured, given the nature or precision of the measurements. Typical, exemplary degrees of error may be within 20%, 10%, or 5% of a given value or range of values. Alternatively, and particularly in biological systems, the terms "about" and "approximately" may mean values that are within an order of magnitude, potentially within 5-fold or 2-fold of a given value. When not explicitly stated, the terms "about" and "approximately" mean equal to a value, or within 20% of that value.

As used herein, numerical quantities are precise to the degree reflected in the number of significant figures reported. For example, a value of 0.1 is understood to mean from 0.05 to 0.14. As another example, the interval of values 0.1 to 0.2 includes the range from 0.05 to 0.24. Thus, a concentration of from 0.1 mg/mL to 2 mg/mL means a concentration range of from 0.05 mg/mL to 2.4 mg/mL.

"Optional" or "optionally" means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

The term "subject" refers to a mammal, such as a domestic pet (for example, a dog or cat), or human. Preferably, the subject is a human.

The phrase "effective amount" refers to the amount which, when administered to a subject or patient for treating a disease, is sufficient to effect such treatment for the disease.

"Treatment" or "treating" includes (1) inhibiting a disease in a subject or patient experiencing or displaying the pathology or symptomatology of the disease (e.g., arresting further development of the pathology and/or symptomatology), (2) ameliorating a disease in a subject or patient that is experiencing or displaying the

pathology or symptomatology of the disease *(e.g.,* reversing the pathology and/or symptomatology), and/or (3) effecting any measurable decrease in a marker of the disease or in a clinical endpoint of the disease, in a disease in a subject or patient that is experiencing or displaying the pathology or symptomatology of the disease.

"Pharmaceutically acceptable salt" includes both acid and base addition salts.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-l,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, />-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Pharmaceutically acceptable base addition salt" refers to those salts which retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Preferred inorganic salts are the ammonium, sodium, potassium, calcium, and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine,

diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine, theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

A "pharmaceutical composition" or "pharmaceutical formulation" refers to a formulation of a chemical compound and a medium generally accepted in the art for the delivery of the biologically active compound to mammals, *e.g.*, humans. Such a medium may include all pharmaceutically acceptable carriers, diluents, or excipients therefor.

"Pharmaceutically acceptable carrier, diluent, or excipient" includes without limitation any adjuvant, carrier, excipient, glidant, sweetening agent, diluent, preservative, dye/colorant, flavor enhancer, surfactant, wetting agent, dispersing agent, suspending agent, stabilizer, isotonic agent, solvent, or emulsifier which has been approved by the United States Food and Drug Administration as being acceptable for use in humans or domestic animals.

The invention disclosed herein is also meant to encompass all pharmaceutically acceptable formulations disclosed herein wherein a chemical compound has been isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, $^{15}0$, $^{17}0$, $^{18}0$, ^{31}P, ^{32}P, ^{35}S, ^{18}F, $^{36}C1$, ^{123}I, and ^{125}I, respectively. Certain isotopically-labelled compounds of structures disclosed herein, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. These radiolabelled compounds could be useful to help determine or measure the effectiveness of the compounds, by characterizing, for example, the site or mode of action, or binding affinity to pharmacologically important site of action. The radioactive isotopes tritium, *i.e.*, ^{3}H, and carbon-14, *i.e.*, ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes, such as deuterium, *i.e.*, ^{2}H, ^{13}C, ^{15}N, or $^{18}0$ may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and

hence are preferred in some circumstances. They are also preferred as internal standards in bioanalytical analyses.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, $^{15}0$ and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Preparations and Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

The invention disclosed herein is also meant to encompass the *in vivo* metabolic products of the disclosed formulations. Such products may result from, for example, the oxidation, reduction, hydrolysis, amidation, esterification, and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising administering a compound of this invention to a mammal for a period of time sufficient to yield a metabolic product thereof. Such products are typically identified by administering a radiolabelled compound of the invention in a detectable dose to an animal, such as rat, mouse, guinea pig, monkey, or to human, allowing sufficient time for metabolism to occur, and isolating its conversion products from the urine, blood or other biological samples. "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The formulations of the invention contain compounds or their pharmaceutically acceptable salts, that may possess one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as *(R)*- or *(S)*- or, as (D)- or (L)- for amino acids. The present invention is meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), *(R)*- and *(S)*-, or (D)- and (L)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds contain olefinic double bonds or other centers of geometric asymmetry, and unless specified

otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

The present invention includes all manner of rotamers and conformationally restricted states of a compound used in the invention. Atropisomers, which are stereoisomers arising because of hindered rotation about a single bond, where energy differences due to steric strain or other contributors create a barrier to rotation that is high enough to allow for isolation of individual conformers, are also included.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose molecules are nonsuperimposeable mirror images of one another.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any of the compounds used in the pharmaceutical formulations disclosed.

The term "concentration" refers to the amount of a pure constituent in a mixture, typically expressed in mg of the pure constituent per mL of volume of the formulation.

The term "physiological pH" refers to the pH typically found in the human body or blood (e.g., at a pH of between about 7.3 and about 7.5).

As used herein, an "amino acid" may be naturally-occurring or non-naturally-occurring.

"Peptide" refers generally to a polymer of amino acids linked by peptide (amide) bonds. It may be of any length and may be linear, branched, or cyclic. The amino acid may be naturally-occurring, non-naturally-occurring, or may be an altered amino acid. This term can also include an assembly of a plurality of polypeptide chains into a complex. This term also includes natural or artificially altered amino acid polymers. Such alteration includes disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation or any other manipulation or alteration. This definition also includes, for example, polypeptides including one or two or more analogs of amino acids *(e.g.,* including non-naturally-occurring amino acids), peptide-like compounds *(e.g.,* peptoids) and other alterations known in the art.

As used herein the term "a functionally equivalent peptide" refers to a peptide that may vary in terms of structure (sequence) but is the same or similar to the original peptide. Functionally equivalent sequence or proteins or peptides may be created via the application of recombinant DNA technology, in which changes in the

protein structure may be engineered, based on considerations of the properties of the amino acids being exchanged. Those skilled in the art may introduce designed changes through the application mutagenesis techniques.

"Tetracosactide" refers to a synthetic form of ACTH, comprising the first twenty-four amino acids of natural human ACTH. Specifically, tetracosactide comprises the amino acid sequence:

H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro-OH (SEQ. ID. NO.: 2).

"Free peptide in solution" as used herein refers to the amount of tetracosactide that remains in the solution (or supernatant) relative to the total amount of tetracosactide in the formulation, typically expressed as a percent. The amount of tetracosactide that remains in the solution refers to the amount of tetracosactide obtained after filtering the solution using a nylon filter having 0.22 micron pore size. The amount of tetracosactide in the formulation refers to the total amount of tetracosactide in the formulation as measured by suitable methods known in the art. For example, the total amount of tetracosactide in the formulation may be measured as the amount after homogenizing the suspension and dissolving the solid portion with acetic acid.

"Insoluble metal-based peptide complexing agent" refers to an insoluble salt of a pharmaceutically acceptable metal that adsorbs a peptide. Examples include zinc hydroxide, zinc phosphate, zinc phosphate hydroxide, aluminum hydroxide, and magnesium aluminum silicate and their hydrates.

A "pharmaceutically acceptable metal" includes alkali metals such as sodium, potassium, and lithium; alkaline earth metals such as calcium and magnesium; transition metals such as zinc; and other metals such as aluminum, bismuth, tin, iron, copper, manganese, cobalt, vanadium, molybdenum, and platinum.

A "metal salt" refers to acids formed by a chemical reaction between a metal and an acid, or a metal and a non-metal.

A "pharmaceutically acceptable metal salt" refers to those metal salts that retain the biological effectiveness and properties of the free metal and that are not biologically or otherwise undesirable.

"Adsorb" or "adsorption" as used herein refers to the adhesion or physical attachment of a molecule suspended in solution to a surface.

The term "substantially free of means that a composition contains little, if any, of a given agent. For example, it may refer to a composition that contains less

than an effective amount of a given agent, such that the amount of the agent would not be sufficient to materially affect the properties of the composition. For example, a pharmaceutical formulation that is "substantially free of a preservative," as used herein, refers to concentrations of preservative about 0.5 mg/mL or less.

"Preservative" refers to a substance added to a composition to prevent decomposition or microbial growth. Examples of preservatives useful in embodiments of the present invention may include phenol, meta-cresol, benzyl alcohol, parabens (methyl, propyl, butyl), benzalkonium chloride, chlorobutanol, thimerosal, and phenylmercuric salts (acetate, borate, nitrate).

"Parenteral administration" refers to delivery of a pharmaceutical composition through external boundary tissue and not by through the digestive tract, typically via injection. Parenteral administration may include epidural (injected into the dura matter (epidural space) of the spinal cord, intravenous (injected into the vein, allowing for immediate adsorption; including IV push, IV piggyback and IV infusion or drip), intramuscular (injected into the muscle), subcutaneous (injected into the fatty layer under the skin), intradermal (injected into the top layer of the skin at a slight angle), intracardiac (injected into the heart), intraocular (injected within the eye), intrathecal (injected into the space surrounding the spinal cord), and intra-articular (injected into the joint) injections. Parenteral administration may involve bolus injection or continuous infusion.

"Sustained release," "long-acting," or "extended release" refers to formulations of a drug wherein the drug is dissolved or released over time, typically at a slower and steadier pace than immediate-release formulations of the same drug.

Pharmaceutical Formulations

As noted above, the present invention relates to pharmaceutical formulations for administering tetracosactide formulations.

The therapeutic effects of ACTH and ACTH analogues, such as tetracosactide, dissolved in aqueous solution are relatively short-lasting following injection. In the past, many attempts to form long-acting, prolonged, or sustained release formulations were unsuccessful (e.g., adsorbing ACTH to aluminum phosphate in colloidal suspensions; adsorbing ACTH to aluminum monostearate suspended in oil). One method of achieving a sustained release ACTH formulation is to form a suspension using a water soluble metal salt (such as zinc chloride) to precipitate an insoluble salt of the metal, for example zinc phosphate, to which the peptide can adsorb. The pH of the solution may be adjusted (e.g., by addition of sodium hydroxide) to a pH of between 6

and 9. A preservative may be added to such a suspension. Such ACTH or ACTH analogue suspensions, when injected intramuscularly or subcutaneously, are resorbed slowly, typically longer than formulations that do not include an insoluble metal-based peptide complexing agent.

In tetracosactide formulations using an insoluble metal-based peptide complexing agent, such as a zinc salt, much of the peptide is non-covalently adsorbed on the surface of the solid, while a smaller portion of the peptide is equilibrated ("free") in solution phase. An equilibrium exists between those two states of the peptide. For example, in a peptide-zinc-phosphate mixture, the equilibrium can be described as follows:

$$a[\text{Peptide}] + b[Zn_x(P0_4)y(OH)_z] \rightleftharpoons [\text{Peptide}]_a\,[Zn_x(P0_4)_y(OH)_z]_b.$$

The solution phase provides the immediate exposure after the injection, while the peptide adsorbed on the surface of the solid zinc-phosphate complex provides a sustained release portion. Without wishing to be bound by any particular theory, it is believed that the addition rate of metal salt and peptide stock solution defines the surface of the insoluble metal-phosphate-hydroxide complex, which affects the amount of free peptide in solution.

Formulations of the present invention comprise an insoluble metal-based peptide complexing agent. The insoluble metal-based peptide complexing agent may contain any pharmaceutically acceptable metal, such as sodium, potassium, magnesium, zinc, aluminum, bismuth, iron, and calcium.

In some embodiments of the invention, the insoluble metal-based peptide complexing agent comprises zinc or aluminum. In some embodiments of the invention, the insoluble metal-based peptide complexing agent is a zinc salt. In still other embodiments of the invention, the insoluble metal-based peptide complexing agent is a zinc-phosphate salt. Embodiments wherein the insoluble metal-based peptide complexing agent is aluminum hydroxide, magnesium aluminum silicate, or their hydrates are also within the scope of the invention.

In some embodiments, the invention comprises a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution. In some embodiments of the invention, the concentration of tetracosactide is from 0.1 mg/mL to 2 mg/mL, from 0.1 mg/mL to 1 mg/mL, or 1 mg/mL.

In still other embodiments, the invention comprises a pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide;

and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4%, less than or equal to 3%, less than or equal to 2%, less than or equal to 1%, less than or equal to 0.5%, or less than or equal to 0.1% of said tetracosactide is present as free peptide in solution.

In still other embodiments, a pharmaceutical formulation for parenteral administration is provided, which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, and said insoluble metal-based complexing agent comprises zinc or aluminum. Embodiments wherein the insoluble metal-based peptide complexing agent is a zinc salt, which in some embodiments is a zinc phosphate salt, are also within the scope of the invention.

In still other embodiments, the invention comprises a pharmaceutical formulation for parenteral administration, which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution , said insoluble metal-based peptide complexing agent is a zinc phosphate salt, and the concentration of zinc is from 0.5 mg/mL to 10 mg/mL, from 1 mg/mL to 5 mg/mL, from 2 mg/mL to 3 mg/mL, or 2.5 mg/mL.

In one embodiment, the invention comprises a pharmaceutical formulation for parenteral administration, which comprises: (a) water for (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein the concentration of tetracosactide is 1 mg/mL, less than or equal to 0.1% of said tetracosactide is present as free peptide in solution, said insoluble metal-based peptide complexing agent is a zinc phosphate salt, the concentration of zinc is 2.5 mg/mL, and the concentration of preservative in the formulation is less than 0.1 mg/mL.

Routes of Administration and Dosing

The pharmaceutical formulations of the present invention are advantageous for parenteral administration, particularly via injection. Generally, formulations suitable for tetracosactide injection may include sterile aqueous solutions (where water soluble) or dispersions, and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. The formulation may be sterile and be fluid to the extent that easy syringeability exists. It may be stable under the conditions of manufacture and storage and be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (such as, glycerol,

propylene glycol, and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, and ascorbic acid. In many cases, it will be preferable to include isotonic agents, for example, sugars, sodium chloride, or polyalcohols such as mannitol and sorbitol, in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

Sterile injectable solutions can be prepared by incorporating the therapeutic compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the therapeutic compound into a sterile carrier which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation include vacuum drying and freeze-drying which yields a powder of the active ingredient *(i.e.,* the therapeutic compound) plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical formulations of the invention may or may not include one or more preservatives. Antimicrobial preservative agents for use in formulations describe herein may include phenol, meta-cresol, benzyl alcohol ($C_6H_5CH_2OH$, BnOH), parabens (methyl, propyl, butyl), benzalkonium chloride, chlorobutanol, thimerosal, and phenylmercuric salts (acetate, borate, nitrate).

The actual dosage amount of the compound administered to a subject may be determined by physical and physiological factors such as age, sex, body weight, severity of condition, the type of disease being treated, previous or concurrent therapeutic interventions, idiopathy of the subject and on the route of administration. These factors may be determined by a skilled artisan. The practitioner responsible for administration will typically determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject.

The pharmaceutical formulations of the present invention are advantageous for parenteral administration, particularly via injection. In some embodiments, the pharmaceutical formulation may be administered by epidural, intravenous, intramuscular, subcutaneous, intradermal, intrathecal, or intra-articular

injection. In one embodiment of the invention, the pharmaceutical formulation described herein is administered via intramuscular injection.

The invention also includes embodiments wherein the formulation for parenteral injection is sterile.

In one embodiment of the invention, the pharmaceutical formulation comprises water as a carrier or dispersion medium for use in a parenteral injection. In certain embodiments the pharmaceutical formulation of the present invention comprises water for injection.

In one embodiment of the invention, the pharmaceutical formulation comprises one or more preservatives. In another embodiment, the formulation is substantially free of a preservative. In still another embodiment, the concentration of a preservative in the formulation is less than 0.1 mg/mL, 0.2 mg/mL, or 0.5 mg/mL. In another embodiment, the formulation is substantially free of benzyl alcohol. In another embodiment, the concentration of benzyl alcohol in the formulation is less than 0.1 mg/mL, 0.2 mg/mL, or 0.5 mg/mL.

Pharmaceutical formulations of the invention may be packaged in a variety of packaging systems, including vials, ampoules, plastic bags, blow-fill-seal containers (bottles and ampoules), 2-chamber vials (AOV), 2-chamber syringes, pre-filled syringes, and cartridges (for devices). These packaging systems may be light and oxygen protective.

Single or multiple doses of the formulation are contemplated. Desired time intervals for delivery of multiple doses can be determined by one of ordinary skill in the art employing no more than routine experimentation. As an example, subjects may be administered two doses daily at approximately 12 hour intervals. In some embodiments, the formulation is administered once a day.

The formulations may be administered on a routine schedule. As used herein a routine schedule refers to a predetermined, designated period of time. The routine schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. For instance, the routine schedule may involve administration twice a day, every day, every two days, every three days, every four days, every five days, every six days, a weekly basis, a monthly basis or any set number of days or weeks there-between. Alternatively, the predetermined routine schedule may involve administration on a twice daily basis for the first week, followed by a daily basis for several months.

In one embodiment of the invention, a human subject is administered daily doses of the formulation that comprise about 1 mg of tetracosactide. In another

embodiment, a human subject is administered does of the formulation that comprise about 1 mg of tetracosactide twice daily. Still other embodiments of the invention include administering about 1 mg of tetracosactide every two, three, four, five, six, seven, or eight days. The invention also includes administering tetracosactide formulations described herein at a dose of 0.5 mg every one, two, or three days. In some embodiments, these dosing regimes are used to administer the formulations to adults.

In another embodiment of the invention, a human subject is administered daily doses of the formulation that comprise about 0.25 to 0.5 mg of tetracosactide. In another embodiment, a human subject is administered does of the formulation that comprise about 0.25 to 0.5 mg of tetracosactide every two, three, four, five, six, seven, or eight days. The invention also includes administering tetracosactide formulations described herein at a dose of 0.5 mg every one, two, or three days. In some embodiments, the human subject is an infant or child.

Methods of Treatment

In one embodiment of the invention the invention comprises a method for treating a subject having a disease amenable to treatment with a pan melanocortin receptor antagonist by administering to a subject in need thereof a pharmaceutical formulation described herein.

In some embodiments, the invention comprises a method for treating a subject having a disease for which the standard of care involves steroid therapy, by administering to a subject in need thereof a pharmaceutical formulation described herein.

In some embodiments, the invention comprises a method for treating infantile spasms (West Syndrome), Idiopathic Membranous Nephropathy, Minimal change disease, deuchenne muscular dystrophy, multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic dermatomyositis, severe erythema multiforme, Stevens-Johnson syndrome, serum sickness, keratitis, iritis, iridocyclitis, diffuse posterior uveitis, choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation, or symptomatic sarcoidosis by administering to a subject in need thereof a pharmaceutical formulation described herein.

In still other embodiments, the invention comprises a method of treating infantile spasms (West Syndrome), Idiopathic Membranous Nephropathy, Minimal

change disease, deuchenne muscular dystrophy, or multiple sclerosis, by administering to a subject in need thereof a pharmaceutical formulation described herein.

In still other embodiments, the invention comprises a method for treating infantile spasms or multiple sclerosis comprising administering to a subject in need thereof a pharmaceutical formulation described herein.

In another embodiment, the invention comprises a method for treating infantile spasms comprising administering to a subject in need thereof a pharmaceutical formulation described herein. In another embodiment, the invention comprises a method for treating infantile spasms comprising administering to a subject in need thereof a pharmaceutical formulation comprising (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, the concentration of tetracosactide is 1 mg/mL, said insoluble metal-based peptide complexing agent is a zinc phosphate salt, the concentration of zinc is 2.5 mg/mL, and the concentration of preservative in said formulation is less than 0.1 mg/mL. In another embodiment, the invention comprises a method for treating infantile spasms comprising administering to a subject in need thereof a pharmaceutical formulation comprising (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 0.1% of said tetracosactide is present as free peptide in solution, the concentration of tetracosactide is 1 mg/mL, said insoluble metal-based peptide complexing agent is a zinc phosphate salt, the concentration of zinc is 2.5 mg/mL, and the concentration of preservative in the formulation is less than 0.1 mg/mL.

In another embodiment, the invention comprises a method for treating multiple sclerosis comprising administering to a subject in need thereof a pharmaceutical formulation described herein. In another embodiment, the invention comprises a method for treating multiple sclerosis comprising administering to a subject in need thereof a pharmaceutical formulation comprising (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution, the concentration of tetracosactide is 1 mg/mL, said metal-based peptide complexing agent is a zinc phosphate salt, the concentration of zinc is 2.5 mg/mL, and the concentration of preservative in the formulation is less than 0.1 mg/mL. In another embodiment, the invention comprises a method for treating multiple sclerosis comprising administering to a subject in need thereof a pharmaceutical formulation comprising (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 0.1% of said tetracosactide is present as free peptide in solution, the

concentration of tetracosactide is 1 mg/mL, said insoluble metal-based peptide complexing agent is a zinc phosphate salt, the concentration of zinc is 2.5 mg/mL, and the concentration of preservative in the formulation is less than 0.1 mg/mL.

In yet another embodiment, a method for treating a disease comprises administering to a subject in need thereof a formulation described herein, wherein the formulation is substantially free of benzyl alcohol and the subject is an infant.

Combination therapy

In addition to being used as a monotherapy, the pharmaceutical formulations may also find use in combination therapies. Effective combination therapy may be achieved with a single composition or pharmacological formulation that includes both agents, or with two distinct compositions or formulations, administered at the same time, wherein one composition includes a compound of this invention, and the other includes the second agent(s). Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to months.

EXAMPLES

EXAMPLE 1

FORMULATION 1

Preparation

A 3 L Bellco flat bottom flask was equipped with a pitch blade impeller and overhead Hi-Torque drive (Bellco Biotech) and addition syringe pump (KD Scientific LEGATO 111). 700 mL deionized water was charged and agitated at 159 rpm. 20 ml of 110 mg/ml $Na_2HPO_4 \cdot 12H_2O$ **(~2.2g)** solution, 62.5 ml of IN NaOH solution, and 20 ml 182 mg/ml NaCl solution were added. A clear solution (stock solution #1) was formed.

Separately, tetracosactide (1.2g) and $ZnCl_2$ (~5.19g) were dissolved in 200 mL of deionized water to form stock solution #2.

Stock solution #2 was charged into the reaction vessel containing stock solution #1 all at once via the side arm of the flask. The resulting white to off-white suspension was agitated for 20 minutes at 159 rpm, resulting in a suspension having a pH of 7.9. An additional 0.5 mL of IN NaOH was added and mixture was agitated for 3 hours at 159 rpm. An additional 1 mL of IN NaOH was added and the mixture was agitated at 100 rpm overnight to result in a white to off-white suspension having a pH of 8.7 (Formulation 1).

Determination of the Amount of Free Peptide in Solution

The amount of free peptide in solution was determined using high-performance liquid chromatography (HPLC). Using a centrifuge tube with a nylon polypropylene filter insert with 0.22 μιτι pores (Costar™ Centrifugal Devices: Spin-X™ LC, 0.22μιη Nylon Polypropylene Tube), 1 mL of the sample suspension was centrifuged at 7,000 RPM for 10 minutes (Fisher Scientific Accuspin Micro 17) to obtain a clear solution (supernatant). The solution was transferred into an HPLC vial and analyzed by HPLC to determine amount of peptide in the solution.

The total peptide in the formulation was measured by first homogenizing the suspension by inverting vial several times, aliquoting a measured portion of the suspension, and adding enough acetic acid to dissolve the solid portion of the formulation. The resulting clear solution was analyzed by HPLC.

HPLC experiments were conducted on a standard HPLC system with Sunfire C18, 250 x 4.6 mm, 5 μm column set to 40°C, while the sample compartment was left at ambient conditions. Injection volume was 30 μΐ, monitoring 277nm wavelength for detection. Two mobile phases were used: Phase A - 0.1% Methanesulfonic acid in water, phase B - 0.1% Methanesulfonic acid in Acetonitrile. Gradient from 99% Phase A to 99% phase B over 45 minutes was used, with a flow rate of 1.0 mL/minute. The approximate retention time of tetracosactide is 23-28 minutes.

Except where explicitly specified, the percent of free peptide in solution typically determined 3 hours to 30 days or more following preparation.

Characterization

Free peptide in solution was determined to be 0.4% of total amount of peptide using procedure described above. Particle size distribution ("PSD") was analyzed using Sympatec HELOS instrument and provided the following values: Xio=17.4, X_{50}=44.4, X_{90}=85.1 microns. Powder X-ray diffraction (PXRD) analysis using CubiX-Pro XRD equipped with a copper X-ray tube (PANanalytical Inc.) powder diffractometer indicated amorphous material, as shown in the PXRD diffractogram of **FIG.** 1.

EXAMPLE 2

FORMULATION 2

Preparation

A similar procedure to that described in Example 1 was used to obtain a formulation having a higher amount of free peptide in solution.

Formulation 2 was prepared using the vessel shown in FIG. 2, which incorporates Millipore filters for sterility and an outlet at the bottom of the flask.

Stock solution #1 was prepared by dissolving 3.08 g of Disodium Phosphate Dodecahydrate (Millipore, NF, 00459502), 5.11g of Sodium Chloride (Granular, Mallinckrodt, USP/EP, 100-105), and 3.72g Sodium Hydroxide (Avantor, NF/EP, 100-107) in 953.3 g of water for injection. After a clear solution was formed, additional water was added to obtain a total weight of 1108.3 g.

Stock solution #2 was prepared by adding 3.10g of Tetracosactide, (BCN peptides, Barcelona, Spain, batch TC1401) and 13.49 g Zinc Chloride, JT Baker, USP, 100-315-030 to 440.4 g of water for injection. After a clear solution was formed, additional water was added to obtain a total weight of 724.8 g.

797.8g of stock solution #1 was filtered through a Millipak 20, 0.22 micron filter into a 3 L Bellco flat bottom flask. 192.2 g of stock solution #2 was filtered through a Millipak 20, 0.22 micron filter into the same vessel using a Watson flexicon liquid filling pump (model 520Di) at a rate of 4 ml/min. An additional 3 hours were allowed for equilibration under stirring rate of 157 rpm, to obtain a suspension (Formulation 2).

Characterization

Free peptide in solution was determined to be 4.0% of total amount of peptide using the HPLC procedure described in Example 1. Formulation 2 also had the following characteristics, determined using the same procedures as described in Example 1: pH = 7.54; amorphous by PXRD, as shown in the PXRD diffractogram of FIG. 3; zinc content 2.322 mg/mL using ICP; particle size measurement: Xio=10.1, X_{50} = 22.4, X_{90} = 54.8 microns.

EXAMPLE 3

FORMULATION 3

Preparation

A 3 L Bellco flat bottom flask was equipped with a pitch blade impeller and overhead Hi-Torque drive (Bellco Biotech), as well as a dosing pump (Watson flexicon liquid filling 520Di), to form a reactor. 600 mL of deionized water was charged into the reactor and agitated at 159 rpm. In a separate container, 2.2g $Na_2HPO_4 \cdot 12H_2O$, 65 ml IN NaOH, and 3.64g NaCl were dissolved in 200 ml water to form stock solution #1.

Stock solution #2 was prepared by dissolving 1.2 g tetracosactide hexaacetate and 5.19g ZnC^ in 200 mL deionized water.

Both stock solutions were dosed into the reactor at 2 ml/min addition rate from the side arms of the reactor using the dosing pump. After the addition, the suspension was left to stir for another 3 hours at 159 rpm, to produce Formulation 3.

Characterization

Free peptide in solution was determined to be undetectable (<0.1%) using the HPLC procedure described in Example 1. The solid portion of the suspension was shown to be amorphous, as shown in the PXRD diffractogram of FlG. 4. The measured pH of the suspension was 9.2.

EXAMPLE 4

ADDITIONAL FORMULATIONS

The methods according to Examples 1 and 2 were modified to produce formulations having various levels of free peptide in solution, shown in Table 1 below:

Table 1

Formulation	Peptide +Zn stock solution addition rate	Peptide in solution (%)	PSD (um)	XRPD
4	10 mL/min	3.7	-	Amorphous
5	10 mL/min	1.3	-	Amorphous
6	5 mL/min	5.5	-	Amorphous
7	4 mL/min	5.2(1 day) 6.8(30 days)	X_{10}=12.0 X_{50}=31.0 X_{90}=74.1	Amorphous
8	4 mL/min	5	-	Amorphous
9	3.5 mL/min	3.8(1 day) 5.8(30 days)	X_{10}=12.0 X_{50}=30.7 X_{90}=72.3	Amorphous

Formulation	Peptide +Zn stock solution addition rate	Peptide in solution (%)	PSD (urn)	XRPD
10	2 mL/min	12.5	Xio=l l .l X_{50}=27.4 X90 =65. 1	Amorphous
11	2 mL/min	11.1	-	Amorphous

Table 1 shows various formulations wherein the second solution formed by mixing tetracosactide with ZnC^ was added to the first stock solution at a particular rate (addition rate). The addition rates included: 10 mL/min, 5 mL/min, 4 mL/min, 3.5 mL/min and 2 mL/min. Amorphous materials were obtained from all addition rates. Except where explicitly specified, the percent of free peptide in solution typically determined 3 hours to 30 days or more following preparation. The percent of free peptide in solution was determined at 1 day and 30 days following preparation for Formulations 7 and 9, as shown.

Using the same procedure as in Example 3, additional exemplary formulations were prepared by adding two stock solutions simultaneously at 2 mL/min. The preparation procedures are summarized in Table 2, along with the characteristics of each resulting formulation. By pre-mixing Na2HP0 $_4$ and NaOH as one stock solution and peptide with ZnC^ as the other stock solution, an amorphous solid phase was produced by adding both solutions simultaneously and the percent of free peptide in solution was 0%.

Table 2

Formulation	Stock solution 1	Stock solution 2	Reactor solution	Peptide in solution (%)	XRPD
3	200 ml (Na_2HPO_4+ NaOH + NaCl)	200 ml (Peptide+$ZnCl_2$)	600 ml H_2O	0	Amorphous
12	400 ml (Na_2HPO_4+ NaOH + NaCl)	400 ml (Peptide+$ZnCl_2$)	200 ml H_2O	0.1	Amorphous
13	200 ml (Na_2HPO_4+ partial NaOH + NaCl)	200 ml (Peptide+$ZnCl_2$)	572 ml H_2O	0.1	Amorphous

Formulation	Stock solution 1	Stock solution 2	Reactor solution	Peptide in solution (%)	XRPD
14	200 ml (Na_2HP0_4 + NaOH + NaCl)	200 ml (Peptide+$ZnCl_2$)	600 ml H_20	0	Amorphous
15	200 ml (Na_2HP0_4 + NaOH)	200 ml (Peptide+$ZnCl_2$)	600 ml NaCl solution	0	Amorphous

EXAMPLE 5

RELATIONSHIP BETWEEN PEPTIDE ADDITION RATE AND CONCENTRATION OF FREE PEPTIDE IN SOLUTION

The formulations shown in Table 1 indicate that the addition rate affects the amount of free peptide, as illustrated in **FIG.** 5. **FIG.** 5 shows the relationship between peptide addition rate (mL/min) and percent of free peptide in solution (%). The results show that increasing the peptide addition rate results in a decrease in the percent of free peptide in solution.

EXAMPLE 6

PHARMACOKINETIC ANALYSES IN RAT MODELS

Pharmacokinetic (PK) analyses for the exemplary formulations Formulation 1 and Formulation 2 were conducted using rat models (total «=12; *n=4* per formulation). Formulations were prepared according to the procedures described in Examples 1 and 2. The percent of free peptide in solution was determined at least 7 days after preparation, for each of the formulations according to the method described in Example 1.

For comparison to other formulations of tetracosactide, the PK properties for Synacthen® Depot (S 1302-09, Novartis Pharmaceuticals Canada, Inc.) were also analyzed. Synacthen® Depot is a tetracosactide formulation for intramuscular delivery containing a tetracosactide zinc phosphate complex and the preservative benzyl alcohol. Two vials of Synacthen® Depot were analyzed for percent free peptide in solution using the HPLC methodology described in Example 1. The percent of free peptide in solution in the two samples was 5.8% and 7.0%, for an average of 6.4%.

Results showing the blood plasma concentration of drug following the administration of Formulation 1 and Formulation 2 are shown in Table 3 and FlG. 6, along with results for Synacthen® Depot. Mean blood plasma levels (averaged over *n=4* per formulation) are shown for each formulation over time. Formulations with

higher free peptide in solution (~4-7% free peptide) had PK properties similar to the reference drug (Synachten® Depot) and exhibited high peak blood plasma concentration of drug after administration (C_{max}). In contrast, Formulation 1, having little free peptide in solution, had lower C_{max} and a higher AUC. Accordingly, Formulation 1 likely results in a longer duration of action, providing an alternative and potentially improved formulation.

Table 3

Formulation	Peptide in solution (%)	AUC (0-infinity) (ng*hr/mL)	C_{max} (ng/mL)
Synacthen® Depot	6.4	7.54	21.25
Formulation 2	4	7.91	9.63
Formulation 1	0.4	10.70	4.11

Formulations having dose concentrations from 0.2 to 1 mg/mL of tetracosactide were tested and performed equivalently to the exemplary formulations when data were normalized (not shown).

All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, including but not limited to U.S. provisional patent application Serial No. 61/121,249 filed February 26, 2015, are incorporated herein by reference, in their entirety. The various embodiments described above can be combined to provide further embodiments. Aspects of the embodiments can be modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments. These and other changes can be made to the embodiments in light of the above-detailed description.

In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation for parenteral administration which comprises: (a) water; (b) tetracosactide; and (c) an insoluble metal-based peptide complexing agent; wherein less than or equal to 4% of said tetracosactide is present as free peptide in solution.

2. A pharmaceutical formulation according to claim 1, wherein the concentration of tetracosactide is from 0.1 mg/mL to 2 mg/mL.

3. A pharmaceutical formulation according to claim 1, wherein the concentration of tetracosactide is from 0.1 mg/mL to 1 mg/mL.

4. A pharmaceutical formulation according to claim 1, wherein the concentration of tetracosactide is 1 mg/mL.

5. A pharmaceutical formulation according to claim 1, wherein less than or equal to 3% of said tetracosactide is present as free peptide in solution.

6. A pharmaceutical formulation according to claim 1, wherein less than or equal to 2% of said tetracosactide is present as free peptide in solution.

7. A pharmaceutical formulation according to claim 1 wherein less than or equal to 1% of said tetracosactide is present as free peptide in solution.

8. A pharmaceutical formulation according to claim 1, wherein less than or equal to 0.5% of said tetracosactide is present as free peptide in solution.

9. A pharmaceutical formulation according to claim 1, wherein less than or equal to 0.1% of said tetracosactide is present as free peptide in solution.

10. A pharmaceutical formulation according to claim 1, wherein said insoluble metal-based peptide complexing agent comprises zinc.

11. A pharmaceutical formulation according to claim 10, wherein said insoluble metal-based peptide complexing agent comprises a zinc salt.

12. A pharmaceutical formulation according to claim 11, wherein said zinc salt is a zinc phosphate salt.

13. A pharmaceutical formulation according to claim 12, wherein the concentration of said zinc is from 0.5 mg/mL to 10 mg/mL.

14. A pharmaceutical formulation according to claim 12, wherein the concentration of said zinc is from 1 mg/mL to 5 mg/mL.

15. A pharmaceutical formulation according to claim 12, wherein the concentration of said zinc is from 2 mg/mL to 3 mg/mL.

16. A pharmaceutical formulation according to claim 12, wherein the concentration of said zinc is 2.5 mg/mL.

17. A pharmaceutical formulation according to claim 1, wherein said formulation is substantially free of a preservative.

18. A pharmaceutical formulation according to claim 17, wherein the concentration of preservative in said formulation is less than 0.5 mg/mL.

19. A pharmaceutical formulation according to claim 17, wherein the concentration of preservative in said formulation is less than 0.2 mg/mL.

20. A pharmaceutical formulation according to claim 17, wherein the concentration of preservative in said formulation is less than 0.1 mg/mL.

21. A pharmaceutical formulation according to claim 1, wherein said formulation is substantially free of benzyl alcohol.

22. A pharmaceutical formulation according to claim 21, wherein the concentration of benzyl alcohol in said formulation is less than 0.5 mg/mL.

23. A pharmaceutical formulation according to claim 21, wherein the concentration of benzyl alcohol in said formulation is less than 0.2 mg/mL.

24. A pharmaceutical formulation according to claim 21, wherein the concentration of benzyl alcohol in said formulation is less than 0.1 mg/mL.

25. A pharmaceutical formulation according to claim 21, wherein the concentration of benzyl alcohol in said formulation is less than 0.05 mg/mL.

26. A pharmaceutical formulation according to claim 1, wherein the concentration of tetracosactide is 1 mg/mL, less than or equal to 0.1% of said tetracosactide is present as free peptide in solution, said insoluble metal-based peptide complexing agent comprises a zinc phosphate salt, the concentration of said zinc is 2.5 mg/mL, and the concentration of preservative in said formulation is less than 0.1 mg/mL.

27. A method for treating a subject having a disease amenable to treatment with a pan melanocortin receptor antagonist comprising administering to a subject in need thereof a pharmaceutical formulation according to any one of claims 1-26.

28. A method for treating a subject having a disease for which the standard of care involves steroid therapy comprising administering to a subject in need thereof a pharmaceutical formulation according to any one of claims 1-26.

29. A method for treating a subject having a disease selected from the group consisting of infantile spasms (West Syndrome), Idiopathic Membranous Nephropathy, Minimal change disease, deuchenne muscular dystrophy, multiple sclerosis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic dermatomyositis, severe erythema multiforme, Stevens-Johnson syndrome, serum sickness, keratitis, iritis, iridocyclitis, diffuse posterior uveitis, choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation, and symptomatic sarcoidosis comprising administering to a subject in need thereof a pharmaceutical formulation according to any one of claims 1-26.

30. A method according to claim 29, wherein said disease is infantile spasms or multiple sclerosis.

31. A method according to claim 29, wherein said disease is infantile spasms.

32. A method according to claim 29, wherein said disease is multiple sclerosis.

A diffractogram showing the X-ray powder diffraction pattern (XRPD) of the solid phase of Formulation 1 (Example 1), indicating that the solid phase is amorphous material.

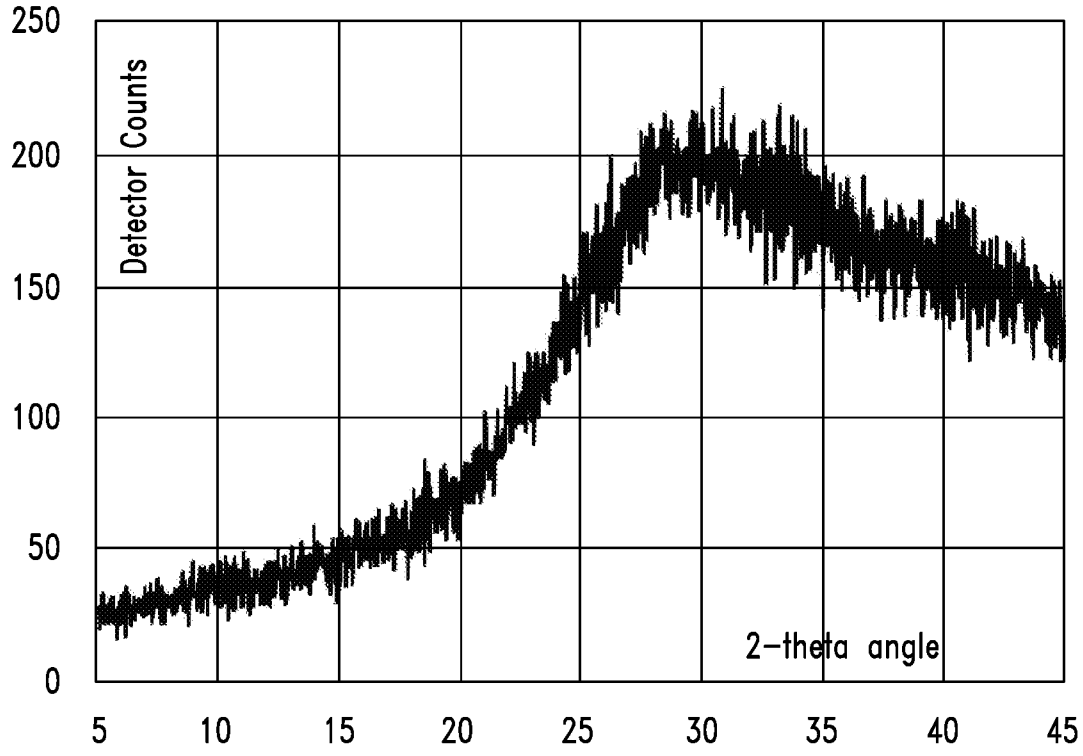

FIG. 1

Vessel assembly diagram used in Example 2.

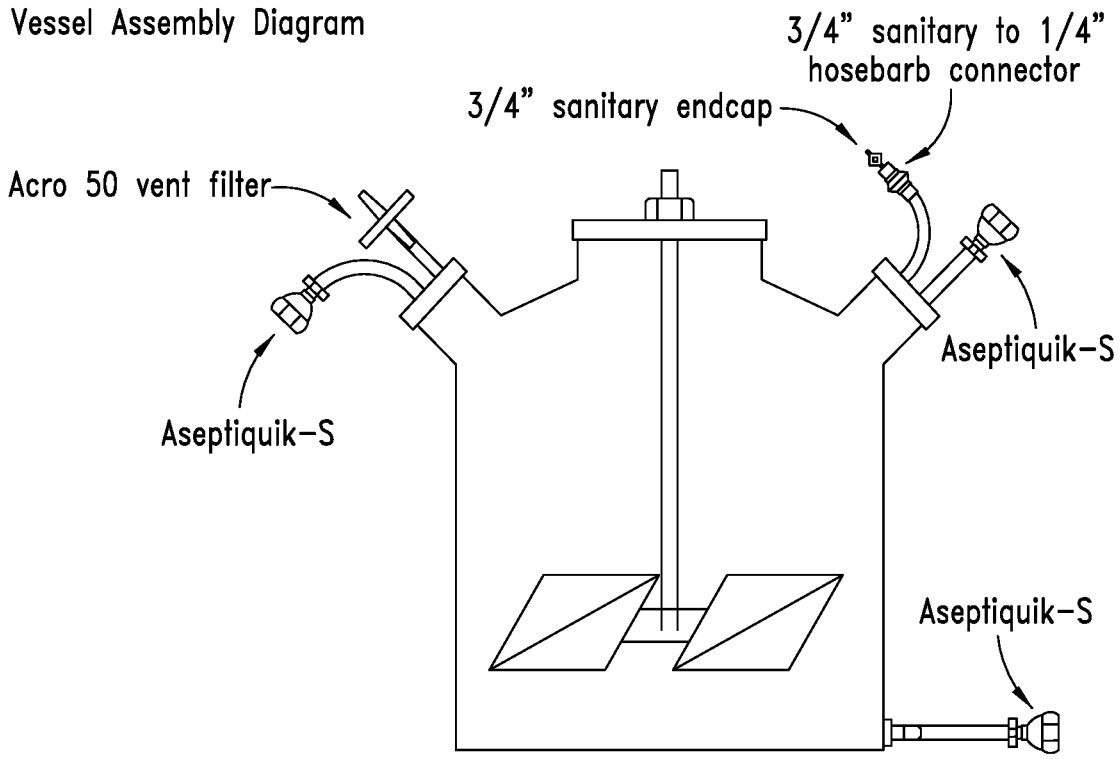

FIG. 2

A diffractogram showing the X-ray powder diffraction pattern (XRPD) of the solid phase of Formulation 2 (Example 2), indicating that the solid phase is amorphous material.

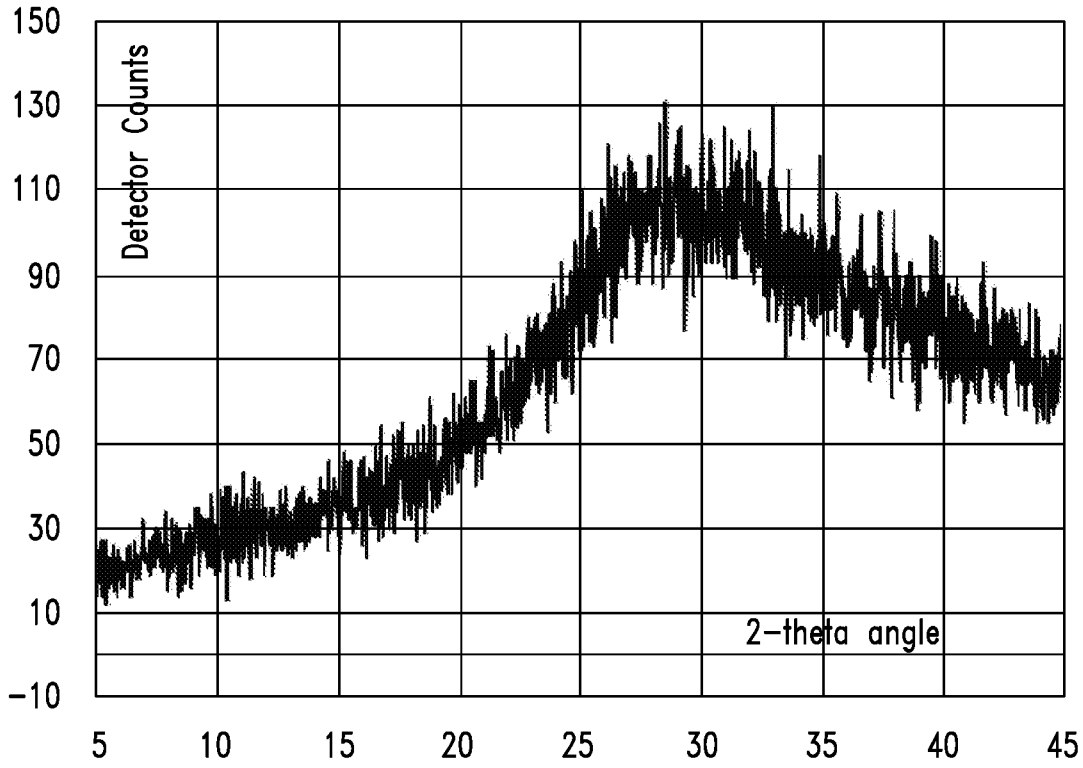

FIG. 3

A diffractogram showing the X-ray powder diffraction pattern (XRPD) of the solid phase of Formulation 3 (Example 3), indicating that the solid phase is amorphous material.

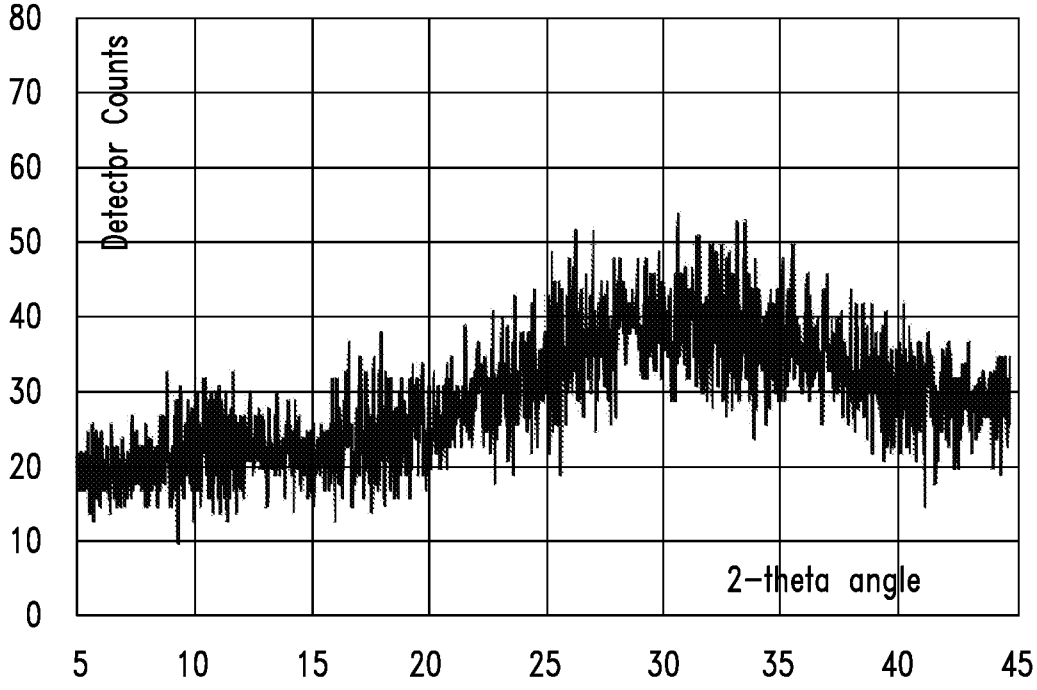

FIG. 4

The relationship between peptide solution addition rate and the percent of free peptide in solution. Several tetracosactide formulations were prepared using the methods described in Examples 1 and 2 (see Table 1). The addition rate of the peptide–zinc solution to the second solution was varied to produce different formulations. The percent of peptide free in solution was lower when faster addition rates were used.

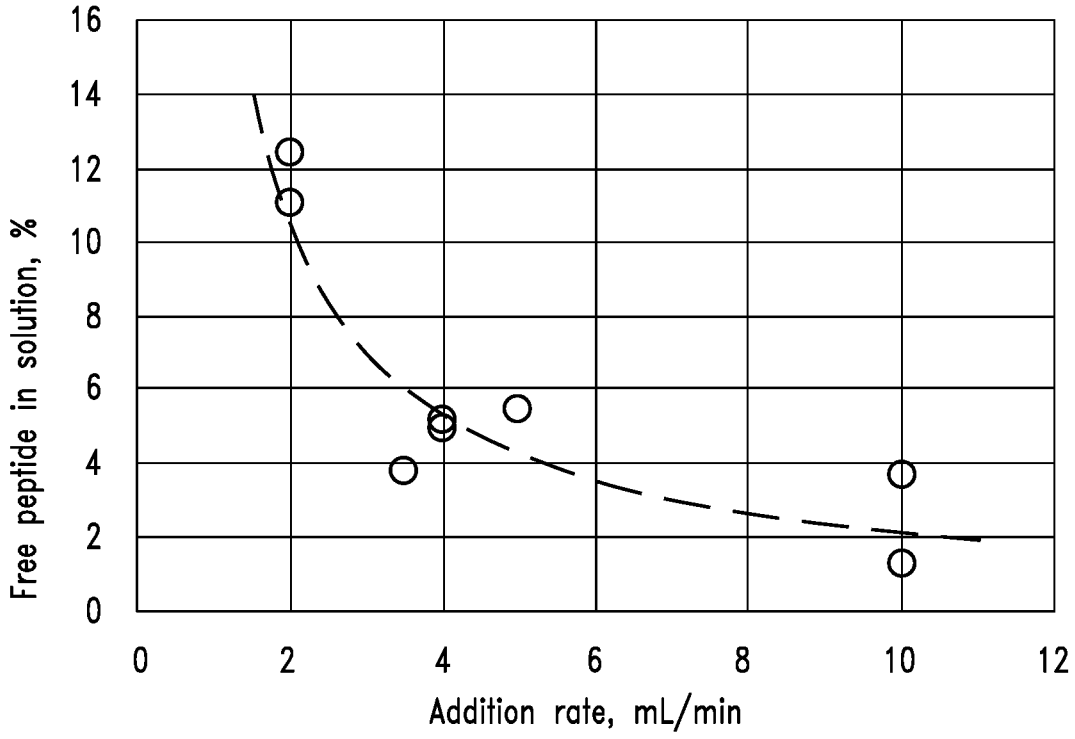

FIG. 5

Mean blood plasma levels of tetracosactide post-intramuscular administration of tetracosactide formulations in rats (n=12 total; n=4 per formulation), showing all data points (a) and showing a subset of the data in greater detail wherein the y-axis has been scaled to a lower maximum value (b).

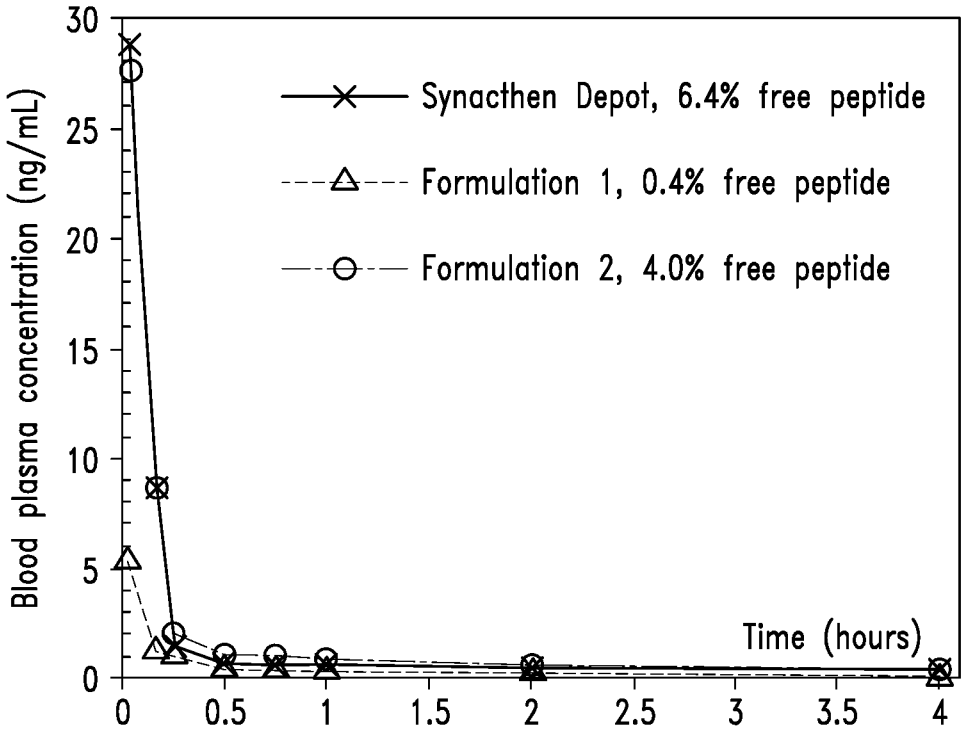

FIG. 6A

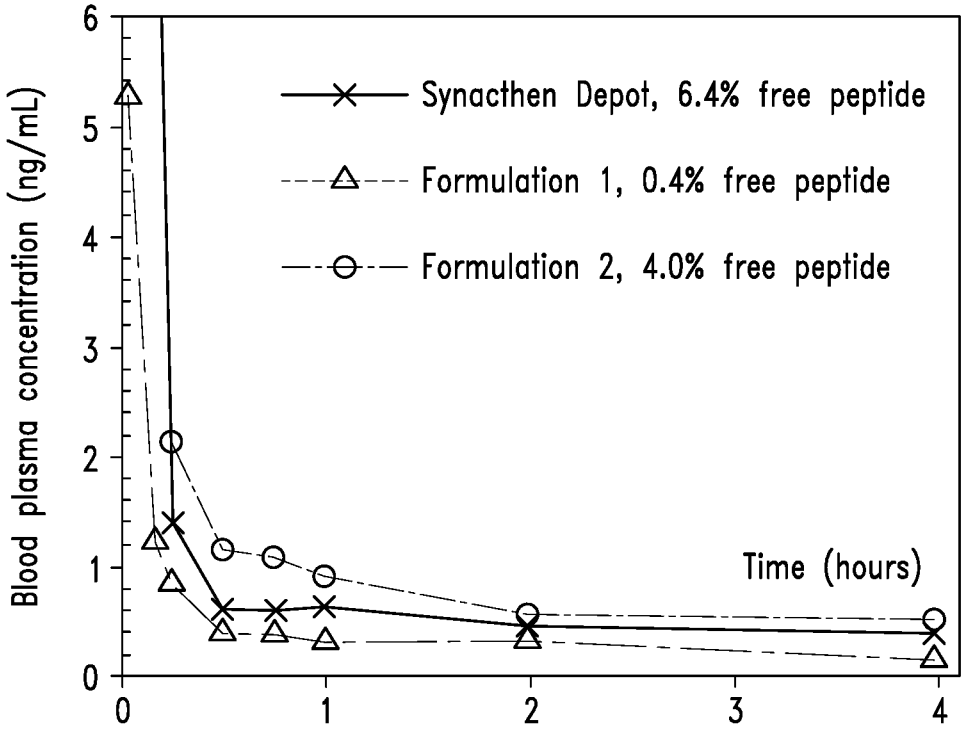

FIG. 6B