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(54) Title: STABLE INJECTABLE COMPOSITION OF PEPTIDE DRUGS AND PROCESS FOR ITS PREPARATION

(57) Abstract: The present invention relates to a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; and processes for its preparation. It is not required to reconstitute the injectable composition of the peptide drug with water prior to administration, thereby rendering it an easy-to-use injectable composition.

STABLE INJECTABLE COMPOSITION OF PEPTIDE DRUGS AND PROCESS FOR ITS PREPARATION

Field of the Invention

The present invention relates to a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; and processes for its preparation.

Background of the invention

In the recent years peptides are widely used as therapeutic agents. Peptides constitute effective therapeutic agents as they exhibit relatively low toxicity as they metabolize to naturally occurring amino acids and at the same time demonstrate high potency and selectivity. In fact, peptide drugs have contributed significantly to the treatment of proliferative disorders such as cancers; metabolic disorders such as diabetes; cardiovascular diseases, osteoporosis, gastrointestinal disorders, bacterial infections, viral infections, acromegaly, and several other diseases.

Despite having many advantages as potential therapeutic agents, peptides have certain limitations as to their uses. For instance, due to their low oral bioavailability and rapid degradation of the peptides by proteolytic enzymes in the gastrointestinal tract, peptides are typically administered by parenteral route. Thus, parenteral administration is one of the most used routes to obtain systemic delivery of peptide drugs. Parenteral composition of peptide drugs has primarily been achieved through aqueous solutions. However, therapeutic peptides are often unstable in the aqueous compositions. Due to the stability problem of many peptides in aqueous solutions, these are commonly formulated as a solid by lyophilization and reconstituted with a sterile diluent prior to administration. Representative examples of peptide drugs that are marketed as lyophilized powder for injection include : (i) Acthrel® (corticorelin ovine triflutate for injection) is a sterile, nonpyrogenic, lyophilized white cake powder, containing corticorelin ovine triflutate, a trifluoroacetate salt of a synthetic peptide that is used for the determination of pituitary corticotroph responsiveness; (ii) Geref® (Sermorelin acetate) is a sterile, non-pyrogenic, lyophilized powder intended for subcutaneous injection after reconstitution with sodium chloride injection, USP. Geref® (sermorelin

acetate for injection) increases plasma growth hormone (GH) concentration by stimulating the pituitary gland to release GH; (iii) Cubicin® (Daptomycin) is supplied as a sterile, lyophilized 500 mg or 350 mg cake that must be reconstituted with sodium chloride prior to use. Daptomycin is a lipopeptide antibiotic which is used in the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive bacteria; and (iv) Cetrotide® (Cetrorelix acetate is supplied as a 0.25 mg or 3 mg sterile lyophilized powder with either 1mL or 3 mL of water for reconstitution in a prefilled syringe. Cetrorelix, a synthetic decapeptide, is a luteinising hormone releasing hormone (LHRH) antagonist.

Compositions including lyophilized compositions for peptide drugs are known in the art. WO2014041425 discloses a lyophilized daptomycin composition comprising an additive selected from the group consisting of pharmaceutically acceptable antioxidants, pharmaceutically acceptable organic acids and pharmaceutically acceptable salts thereof, pharmaceutically acceptable glucose derivatives and pharmaceutically acceptable salts thereof, and combinations thereof.

WO2011063419 discloses a solid daptomycin preparation with improved reconstitution time and stability profile.

WO2014045296 discloses a lyophilized pharmaceutical composition comprising antibacterial agent, daptomycin and tocopheryl phosphate hydrolysate mixture with improved reconstitution time for parenteral administration and also discloses a process for its preparation.

WO2012077131 discloses a stable aqueous pharmaceutical preparation containing cetrorelix or its pharmaceutically acceptable salt in the form of ready-to-use solutions avoiding reconstitution step prior to use and process for preparing such preparations. The examples disclosed illustrate that water is an essential ingredient of the composition.

From the above discussion it is apparent that currently marketed compositions of peptide drugs are primarily in the form of aqueous or lyophilized compositions. However, peptides may undergo several degradation pathways when they are formulated in aqueous solution. The presence of water in the composition can lead to deterioration of the peptide because of hydrolysis. Therefore, it is desirable to develop a stable composition for peptides and for the purpose non-aqueous based composition would be

appropriate for peptides. To overcome stability problem, it is essential to find a non-aqueous solvent system in which the peptides have adequate solubility and stability.

Thus, there exists a need for the development of a new or an improved composition for therapeutic peptides that would prevent degradation, yet increase solubility and stability of the peptides. Moreover, there is a need to provide a stable and ready-to-use injectable composition of therapeutic peptides to improve patient compliance.

As stated above use of aqueous solution in case of compositions of peptide based actives has been a challenging task due to degradation of peptide and impurity generation, which in turn makes the injection preparation unstable.

In consideration of the need as indicated above, inventors of the present invention have done extensive research and conducted several experiments to develop a stable, non-aqueous and ready-to-use injectable composition of therapeutic peptides, without a need to reconstitute with water prior to administration, thereby rendering the composition according to the present invention an easy-to-use injectable composition. The inventors have also provided a simple and cost-effective process for the preparation of the stable, non-aqueous and ready-to-use composition of peptide(s).

Summary of the invention

In one aspect, the present invention provides a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said injectable composition comprises:

(i) a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said peptide drug is other than bivalirudin;
(ii) a non-aqueous solvent system;
(iii) optionally a polyol;
(iv) optionally a pH adjusting agent; and
(v) optionally an antioxidant.

In one aspect, the present invention provides a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said injectable composition comprises:

(i) a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said peptide drug is other than bivalirudin;

(ii) a non-aqueous solvent system consisting of a primary non-aqueous solvent and optionally one or more secondary non-aqueous co-solvent (s);

(iii) optionally a polyol;

(iv) optionally a pH adjusting agent; and

(v) optionally an antioxidant.

In another aspect, the present invention provides a process for the preparation of a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof.

In further aspect, the present invention provides a method for treating or preventing one or more diseases, disorders or conditions, comprising administering to a subject in need thereof; a stable, non-aqueous and ready-to-use injectable composition of the present invention in an amount effective to treat or prevent the conditions, diseases or disorders.

In another aspect, the present invention provides a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; for the manufacture of a medicament for use in the treatment or prevention of one or more diseases, conditions or disorders.

In another aspect, the present invention provides a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; for use in the treatment of a subject having one or more diseases, conditions or disorders.

In still further aspect, the present invention provides a pharmaceutical kit comprising: (a) an injectable composition comprising a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; a non-aqueous solvent system consisting of a primary non-aqueous solvent and optionally one or more secondary non-aqueous co-solvent(s); optionally a polyol, optionally a pH adjusting agent and optionally an antioxidant; and (b) optionally a package insert comprising instructions for using the said injectable composition.

These and other aspects and advantages of the present invention will be apparent to those skilled in the art from the following description.

Detailed Description of the Invention

It should be understood that the detailed description and specific examples, while indicating embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art. One skilled in the art, based upon the definitions herein, may utilize the present invention to its fullest extent. The following specific embodiments are to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Unless otherwise defined, all the terms used herein, including the technical and scientific terms, have the meaning as that generally understood by one of ordinary skill in the art to which the present invention relates.

Definitions:

For the purpose of the disclosure, listed below are definitions of various terms used to describe the present invention. Unless otherwise indicated, these definitions apply to the terms as they are used throughout the specification and the appended claims, either individually or as part of a larger group. They should not be interpreted in the literal sense. They are not general definitions and are relevant only for this application.

It should be noted that, as used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise.

It should be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise.

As used herein, the term "about" means approximately and in the context of numerical values the term “about” can be construed to estimate a value that is ±10% of the value or range recited.

Within the context of the present invention the term “stable” as used herein in reference to the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; means that the said composition does not exhibit

appreciable degradation upon storage over a set time limit, at a set temperature, and at an identified pH or within the context of the present invention the term "stable" as used herein in reference to the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; means that the said composition exhibit a chromatographic purity, where in the impurities identified are within the acceptable limit.

Within the context of the present invention, the term "sterile composition" means one in which essentially all forms of microbial life have been destroyed by an appreciable amount to meet the sterilization criteria outlined in the US Pharmacopeia.

Within the context of the present invention, the term "ready-to-use" or "RTU" as used herein in reference to the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; is a non-aqueous, injectable composition that is stable and is not reconstituted from a lyophilizate. The term "RTU" also encompasses within its scope, non-aqueous, injectable composition that is stable and has been diluted from a concentrated, liquid solution just prior to use.

Within the context of the present invention the term "non-aqueous composition" as used herein means a composition with not more than 2 % water content.

The term "non-aqueous solvent" means a non-polar solvent which contain bonds between atoms of similar electronegativity like carbon and hydrogen by which they lack partial charges and do not contain hydrogen attached to oxygen or nitrogen so that they are unable to form hydrogen bonds with themselves. Examples of solvents are selected from the group but not limited to ethylene glycol, polyethylene glycols (PEGs), ethylene glycol, propylene glycol (PG), dipropylene glycol, tripropylene glycol, polyvinylpyrrolidone (PVP), methoxy propylene glycol (MPEG), glycerol, glycofurol or a mixture thereof.

The term "non-aqueous RTU composition" means the composition is devoid of any water content in the final finished product or during process for preparation of the same. However, a negligible amount i.e. not more than 2% of water or moisture may be present due to external environmental factors which does not have any impact on the physiochemical property, specifically on the stability of the composition.

As used herein, the term "has not been reconstituted from a lyophilizate" means that a solid has not been dissolved or suspended.

The term "pharmaceutically acceptable excipient" as used herein means a diluent, carrier, or composition auxiliary, which is non-toxic, and inert, which does not have undesirable effects on a subject to whom it is administered and is suitable for delivering a therapeutically active agent (e.g. peptide drug) to the target site without affecting the therapeutic activity of the said active agent.

The term "pharmaceutically acceptable salt" or "pharmaceutically acceptable salt(s)" means salt(s) of the peptide drug(s), which can be prepared by treating the peptide drug(s) with an appropriate acid or a base. Examples of pharmaceutically acceptable base addition salts include, but are not limited to, sodium, potassium, calcium, magnesium, ammonium salts or inorganic base salt. Examples of pharmaceutically acceptable organic base addition salts include, but are not limited to, those derived from organic bases such as lysine, arginine, guanidine, and the like. Examples of pharmaceutically acceptable acid addition salts include, but are not limited to, those derived from inorganic acids such as hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid and the like, as well as the salts derived from organic acids such as acetic acid, trifluoroacetic acid, propionic acid, oxalic acid, maleic acid, benzoic acid, succinic acid, fumaric acid, phthalic acid, benzenesulfonic acid, p-toluenesulfonic acid, citric acid, tartaric acid, methanesulfonic acid and the like.

The term "co-crystal" refers to a crystalline structure made up of two or more components in a definite stoichiometric ratio, where each component is defined as either an atom, ion, or molecule. The term co-crystal" encompasses within its scope many types of compounds, including hydrates, solvates and clathrates.

The term "composition" or "injectable composition" refers to a unit dose or a multi dose of an active pharmaceutical ingredient and a pharmaceutically acceptable excipient, which can be prepared by the processes described in one or more embodiments of the present invention. In the context of the present invention, the terms "composition", "injectable compositions" and "stable, non-aqueous and ready-to-use injectable composition" are used interchangeably. In the case of the injectable composition of the present invention, the active pharmaceutical ingredient is a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof.

The term "polyol" as used herein, refers to an alcohol containing multilple hydroxyl groups. Polyols may comprise, but are not limited to, glycerin, sucrose, lactose,

glucose, fructose, arabinose, xylose, ribose, mannose, galactose, dextrose, sorbose, sorbitol, mannitol, maltose, cellobiose, xylitol, or a combination thereof.

The term "stirring" encompasses within its scope, sonication or turbulence or agitation by other means. Therefore the term "stirring" can be interchangeably used with the terms "sonication", "turbulence" or "agitation".

As used herein, the term "pH" is a measure of hydrogen ion concentration, as commonly used in the art. Customarily the pH provides a measure on a scale from 0 to 14 of the acidity or alkalinity of a solution. In the context of the present invention, the pH of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof, of the present invention is between about 2.0 and about 11.0.

The term "pH adjusting agent" or "pH adjusting agents" as used herein, includes a substance that adjusts the pH of pharmaceutical compositions to intended pH. Customarily, the pH adjusting agents may include pharmaceutically acceptable acids, bases, or buffering agents. For example, the acids may include, but are not limited to, one or more inorganic mineral acids such as citric, fumaric, gluconic, lactic, malic, metatartaric, tartaric, ascorbic and benzene sulphonic acid and the like. In the context of the present invention, the pH adjusting agent may be a base or a buffering agent. The bases may be one or more inorganic bases or organic bases, including, but not limited to, alkaline carbonate, alkaline bicarbonate, alkaline earth metal carbonate, alkaline hydroxide, alkaline earth metal hydroxide or amine. For example, the inorganic or organic base may be an alkaline hydroxide such as lithium hydroxide, potassium hydroxide, cesium hydroxide, sodium hydroxide or the like; an alkaline carbonate such as calcium carbonate, sodium carbonate or the like; or an alkaline bicarbonate such as sodium bicarbonate or the like; the organic base may also be sodium acetate. The buffering agent can be, but is not limited to an alkali metal salt of an amino acid, aluminum hydroxide, aluminum magnesium hydroxide, aluminum glycinate, calcium acetate, calcium bicarbonate, calcium borate, calcium carbonate, calcium citrate, calcium gluconate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium phthalate, calcium phosphate, calcium succinate, calcium tartarate, dibasic sodium phosphate, dipotassium hydrogen phosphate, dipotassium phosphate, disodium hydrogen phosphate, disodium succinate, magnesium acetate, magnesium aluminate, magnesium borate, magnesium bicarbonate, magnesium carbonate, magnesium citrate, magnesium

gluconate, magnesium hydroxide, magnesium lactate, magnesium metasilicate aluminate, magnesium oxide, magnesium phthalate, magnesium phosphate, magnesium silicate, magnesium succinate, magnesium tartarate, potassium acetate, potassium carbonate, potassium bicarbonate, potassium borate, potassium citrate, potassium metaphosphate, potassium phthalate, potassium phosphate, potassium polyphosphate, potassium pyrophosphate, potassium succinate, potassium tartarate, sodium acetate, sodium bicarbonate, sodium borate, sodium carbonate, sodium citrate, sodium gluconate, sodium hydrogen phosphate, sodium lactate, sodium phthalate, sodium phosphate, sodium polyphosphate, sodium pyrophosphate, sodium sesquicarbonate, sodium succinate, sodium tartarate, sodium tripolyphosphate, tetrapotassium pyrophosphate, tetrasodium pyrophosphate, tripotassium phosphate, trisodium phosphate, or a mixture thereof.

A relative pH has been measured because it is difficult to measure the absolute pH of a non-aqueous solution due to lack of hydrogen ion activity or concentration. Further, the pH of the composition may vary depending upon the type of instrument and dilution media.

In the context of the invention the term "solvent system" refers to a primary solvent and optionally one or more secondary solvent selected from a group of solvents.

Within the context of the present invention, the term "antioxidants" means a substance which is particularly used because certain compounds suitable for use in compositions of the invention are prone to degradation by autoxidation. Antioxidants may comprise, but are not limited to, acetylcysteine, ascorbyl palmitate, butylated hydroxyanisole ("BHA"), butylated hydroxytoluene ("BHT"), monothioglycerol, potassium nitrate, ascorbic acid or sodium ascorbate, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium bisulfite, vitamin E or a derivative thereof, propyl gallate, edetate ("EDTA") (e.g., disodium edetate), diethylenetriaminepentaacetic acid ("DTPA"), triglycollamate ("NT"), DL- or D-α-tocopherol, DL- or D-α-tocopheryl acetate or a combination thereof. Antioxidants may also comprise amino acids such as methionine, histidine, cysteine and those carrying a charged side chain, such as arginine, lysine, aspartic acid, and glutamic acid. Any stereoisomer (e.g., L-, D-, or a combination thereof) of any particular amino acid (e.g., methionine, histidine, arginine, lysine, isoleucine, aspartic acid, tryptophan, threonine and combinations thereof) or

combinations of these stereoisomers, is also encompassed within the scope of the term "antioxidant" so long as the amino acid is present either in its free base form or its salt form. The antioxidant, if present, may be added to compositions in accordance with the invention in an amount of up to, for example, 0.05% (w/v), preferably from 0.001 to 1%. Within the context of the present invention and as used herein, the term "peptide drug" or "peptide drug(s)" refers to synthetic or biological compounds (and salts thereof) containing short chains of amino acids bound together by amide (CONH) linkages that have demonstrated or potential use in treating, preventing, or ameliorating one or more diseases, disorders, or conditions in a subject in need thereof. The term "peptide drug(s)" is used herein interchangeably with the terms "therapeutic peptide(s)" and "peptide(s)". Typically, the peptide drugs are short chains of amino acid monomers containing up to 50 amino acids bound together by amide (CONH) linkages and have a molecular weight of less than approximately 5000 Daltons. Peptides can be classified by function and also by synthesis. Some common types of peptides classified by function include hormones, neuropeptides, and alkaloids. When classified by synthesis, peptides can be milk peptides ribosomal, non-ribosomal, and peptonic. Depending on the number of amino acids, peptides are called dipeptides, tripeptides, tetrapeptides, and conjugated peptides which contain amino acid and prosthetic group such as cyclopeptide, glycopeptide, chromopeptide, lipopeptide, nucleopeptide and phosphopeptide.

Further, in the context of the present invention, the peptide drug is other than bivalirudin. Representative examples of peptide drugs include, but are not limited to, daptomycin, nesiritide, cetrorelix acetate and a combination thereof. Combinations of peptide drugs with other drugs such as proteins, small molecules and the like are also encompassed within the scope of the present invention. Within the context of the present invention and as used herein the term "protein drug" or "protein drug(s)" refers to hormones, enzymes and/or antibodies that are naturally occurring, recombinant or chemically synthesized large biological molecules or macromolecules comprising a plurality of natural or modified amino acids residues bound together by amide (CONH) linkages. Within the context of the present invention and as used herein the term "small molecule drug" or "small molecule drug(s)" refers to therapeutically active compounds (and/or salts thereof) having molecular weight of less than about 3000 Daltons, that can bring about a desired and/or beneficial therapeutic effect on a subject in need thereof.

As used herein, the term "absolute alcohol" refers to ethanol containing from about 98.0 to 99.8 v/v/ % of ethanol and from about 0.2 to 2.0 v/v % of water.

Within the context of the present invention and as used herein the term "subject" refers to an animal, preferably a mammal, and most preferably a human. In the context of the present invention, the term "mammal" is used interchangeably with the term "patient" or "subject". In the context of the present invention the phrase "a subject in need thereof" means a subject (patient) in need of the treatment of one or more diseases, conditions or disorders (as described herein) for which a peptide drug can be suitably used.

Injectable composition:

As discussed herein above, the inventors of the present invention have done extensive research and conducted several experiments to develop a stable injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof which can be prepared in a solubilized and stable form suitable for ready-to-use injection.

Further, being a RTU composition, it has enhanced patient compliance and also provides a more stable, safe and effective composition when compared to currently marketed lyophilized compositions.

In respect of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; of the present invention, there is no requirement of reconstituting the composition with water prior to its administration, thus eliminating tedious task of reconstitution step in aseptic area, thereby providing an easy-to-use injectable composition.

The injectable composition of the present invention can be used for a wide variety of peptide drugs.

Accordingly, in one aspect, the present invention relates to a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said injectable composition comprises:

(i) a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein said peptide drug is other than bivalirudin;

(ii) a non-aqueous solvent system consisting of a primary non-aqueous solvent, optionally one or more secondary non-aqueous co-solvent(s);

(iii) optionally a polyol;

(iv) optionally a pH adjusting agent; and

(v) optionally an antioxidant.

In an embodiment, the peptide drug is a peptide containing up to 50 amino acids.

In an embodiment, the peptide drug is selected from but not limited to calcitonin, leptin, melatonin, nafarelin, leuprolide, interferon-alpha, interferon-beta, interferon-gamma, low molecular weight heparin, imitrex, integrelin, nesiritide, nemifitide, sandostatin, cetrorelix, ganirelix, sermorelin , zafirlukast, exanitide, pramlintide, vasopressin, desmopressin, glucagon, oxytocin, corticorelin ovine triflutate, corticotropin releasing hormone, daptomycin, tobramycin, triptorelin, goserelin, fuzeon, hematide, buserelin, octreotide, gonadorelin, felypressin, deslorelin, vasopressin, eptifibatide, interleukin11, endostatin, angiostatin, N-acetyl oxyntomodulin 30-37, oxyntomodulin, ularitide, human Corticotropin-Releasing Factor (hCRF or xerecept®), secretin, thymopentin, neuromedin U, neurotensin, elcatonin, antide, dynorphin A (1-13), sincalide, thymopentin, thymosin alpha1 (thymalfasin), fertirelin, hisrelin, thymalfasin, ecallantide, oxycortin, urocortin, arixtra, urocortin, amylin, melanotan, valpreotide; and their pharmaceutically acceptable salts.

In an embodiment, the peptide drug is selected either singly or in combination from daptomycin, nesiritide or cetrorelix; or a pharmaceutically acceptable salt thereof.In an embodiment, the injectable composition contains peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; at a concentration in the range of about 1 mg/mL to about 200 mg/mL.

In an embodiment, the injectable composition contains peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; at a concentration in the range of about 5 mg/mL to about 80 mg/mL.

In an embodiment, the injectable composition contains peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; at a concentration of about 50 mg/mL.

In an embodiment, the non-aqueous solvent system comprises 100% primary non-aqueous solvent; or in the non-aqueous solvent system, the primary non-aqueous solvent

and the secondary non-aqueous co-solvent can be used in a ratio ranging from about 99:1 to about 50:50.

In an embodiment, the non-aqueous solvent system comprises 100% primary non-aqueous solvent.

In an embodiment, in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent can be used in the ratio ranging from about 99:1 to about 50:50.

In an embodiment, in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent can be used in the ratio of 99:1, 95:5, 90:10, 85:15, 80:20, 70:30, 60:40 or 50:50.

In an embodiment, in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent can be used in the ratio of 90:10.

In an embodiment, in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent can be used in the ratio of 85:15.

In an embodiment, the non- aqueous solvent system comprises one or more solvent(s) selected from the group consisting of but not limited to ethylene glycol, ethylene glycol, propylene glycol, glycerol, polyethylene glycol, dipropylene glycol, tripropylene glycol, methanol, ethanol, absolute alcohol, 1-propanol and isopropanol (isopropyl alcohol) or a mixture thereof.

In an embodiment, the primary non-aqueous solvent contained in the non-aqueous solvent system is selected from the group consisting of but not limited to ethylene glycol, propylene glycol, dipropylene glycol, tripropylene glycol, glycerol and polyethylene glycol or a mixture thereof.

In an embodiment, the primary non-aqueous solvent is propylene glycol.

In an embodiment, the optional secondary non-aqueous co-solvent(s) contained in the non-aqueous solvent system is a (C_1-C_3)alkyl alcohol selected from the group consisting of but not limited to methanol, ethanol, absolute alcohol, 1-propanol and isopropanol (isopropyl alcohol) or a mixture thereof.

In an embodiment, the optional secondary non-aqueous co-solvent contained in the non-aqueous solvent system is isopropyl alcohol, ethanol or absolute alcohol; or a combination thereof.

In an embodiment, the optional secondary non-aqueous co-solvent(s) contained in the non-aqueous solvent system is ethanol or absolute alcohol.

In an embodiment, the optional secondary non-aqueous co-solvent contained in the non-aqueous solvent system is ethanol.

In another embodiment, the optional secondary non-aqueous co-solvent contained in the non-aqueous solvent system is absolute alcohol.

In another embodiment, the optional secondary non-aqueous co-solvent contained in the non-aqueous solvent system is isopropyl alcohol.

In another embodiment, the optional secondary non-aqueous co-solvent(s) contained in the non-aqueous solvent system is a combination of ethanol/absolute alcohol and isopropyl alcohol.

In an embodiment, the polyol is selected from a group consisting of but not limited to glycerin, sucrose, lactose, glucose, fructose, arabinose, xylose, ribose, mannose, galactose, dextrose, sorbose, sorbitol, mannitol, maltose, cellobiose, xylitol, trehalose or a combination thereof.

In an embodiment, the polyol is in the range of about 0.01% to about 10% of the total injectable composition of a peptide drug.

In an embodiment, the polyol is sorbitol or racemic salts or isomers thereof.

In an embodiment, the polyol is D-sorbitol.

In the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof, the primary non-aqueous solvent, the secondary non-aqueous co-solvent and the polyol are present in an amount such that peptide drug at the concentration of at least 50 mg/ml peptide drug is completely soluble and stable in the injectable composition.

In an embodiment, the non-aqueous solvent system contains propylene glycol and ethanol.

In an embodiment, the non-aqueous solvent system contains propylene glycol and absolute alcohol.

In an embodiment, the non-aqueous solvent system contains propylene glycol and isopropyl alcohol.

In an embodiment, the non-aqueous solvent system comprises 100% propylene glycol; or in the non-aqueous solvent system, the propylene glycol and the

ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in a ratio ranging from about 99:1 to about 50:50.

In an embodiment, the non-aqueous solvent system comprises 100% propylene glycol.

In an embodiment, in the non-aqueous solvent system, the propylene glycol and the ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in the ratio ranging from about 99:1 to about 50:50.

In an embodiment, in the non-aqueous solvent system, the propylene glycol and the ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in the ratio of 99:1, 95:5, 90:10, 85:15, 80:20, 70:30, 60:40 or 50:50.

In an embodiment, non-aqueous solvent system consisting of propylene glycol and ethanol//absolute alcohol (and/or isopropyl alcohol) can be used in the ratio of 90:10.

In an embodiment, non-aqueous solvent system consisting of propylene glycol and ethanol//absolute alcohol (and/or isopropyl alcohol) can be used in the ratio of 85:15.

In another embodiment, the pH adjusting agent is selected from pharmaceutically acceptable acids, bases, or buffering agents.

In another embodiment, the pH of the ready-to-use peptide drug injectable composition of the present invention is between about 2.0 and about 11.0.

In another embodiment, the pH of the ready-to-use peptide drug injectable composition of the present invention is between about 4.0 and about 8.0.

In another embodiment, the pH of the ready-to-use peptide drug injectable composition of the present invention is between about 4.0 and about 5.5.

In an embodiment, the antioxidants may be selected from butylated hydroxytoluene, sodium metabisulphite acetylcysteine, ascorbyl palmitate, butylated hydroxyanisole, monothioglycerol, potassium nitrate, ascorbic acid or sodium ascorbate, sodium formaldehyde sulfoxylate, sodium bisulfite, vitamin E or a derivative thereof, propyl gallate, edetate, diethylenetriaminepentaacetic acid, triglycollamate, DL- or D-α-tocopherol, DL- or D-α-tocopheryl acetate, amino acids, stereoisomers of amino acids; or a combination thereof.

In another embodiment, the antioxidant may be selected from butylated hydroxytoluene or sodium metabisulphite.

Process for the preparation of injectable composition:

In an aspect, the present invention relates to a process for the preparation of a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said process comprises the steps of:

a) dissolving a pH adjusting agent in a non-aqueous solvent system consisting of a primary non-aqueous solvent to obtain a first solution by stirring the solution at a temperature ranging from 2°C to 60°C over a period of 30 minutes to 120 minutes and allowing the solution to attain the temperature of 2°C to room temperature;

b) optionally adding polyol and antioxidant to the secondary non-aqueous co-solvent under constant stirring until the polyol dissolves to obtain a second solution;

c) adding the second solution of step (b) to the first solution of step (a) under constant stirring to obtain a third solution;

d) dispersing the peptide drug in the third solution of step (c) to obtain a clear solution;

e) optionally filtering the solution of step (d); and

f) filling the clear solution of step (e) into a container to obtain a preparation in a ready-to-use form.

In an embodiment, the present invention relates to a process for the preparation of a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said process comprises the steps of:

a) dissolving polyol, optionally antioxidant and pH adjusting agent in secondary non-aqueous co-solvent to obtain a first solution by stirring the solution at a temperature ranging from 2°C to 60°C over a period of 30 minutes to 120 minutes and allowing the solution to attain the temperature of 2°C to room temperature;

b) adding primary non-aqueous solvent to the first solution of step (a) to obtain a second solution;

c) adding peptide drug to the second solution of step (b) and allowing to disperse to produce a solution;

d) optionally filtering the solution of step (c) one or more times to obtain a clear solution; and

e) filling the clear solution of step (d) into a container to obtain a composition in a ready-to-use form.

In an embodiment, the present invention relates to a process for the preparation of the stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said process comprises the steps of:

a) dissolving a pH adjusting agent in a non-aqueous solvent system consisting of a primary non-aqueous solvent to obtain a mixture and stirring the resulting mixture at a temperature ranging from 2°C to 60°C over a period of 30 minutes to 120 minutes to obtain a first solution;

b) allowing the resulting first solution of step (a) to attain a temperature of 2°C to room temperature;

c) optionally adding polyol and antioxidant to the first solution of step (b) under constant stirring until the polyol dissolves, to obtain a second solution;

d) optionally adding a secondary non-aqueous co-solvent to the second solution of step (c) under constant stirring for 5 minutes to 10 minutes to obtain a third solution;

e) adding peptide drug to the third solution of step (d) and allowing to disperse to obtain a solution;

f) optionally filtering the solution as obtained in step (e) one or more times to obtain a clear solution; and

g) filling the clear solution of step (f) in suitable containers to obtain a composition in a ready-to-use form.

In an embodiment, the present invention relates to a process for the preparation of the stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a

pharmaceutically acceptable salt or a co-crystal thereof; wherein the said process comprises the steps of:

a) dissolving polyol, optionally antioxidant and pH adjusting agent in primary non-aqueous solvent to obtain a solution by stirring the resulting mixture at a temperature ranging from 2°C to 60°C over a period of 30 minutes to 120 minutes to obtain a first solution;

b) allowing the resulting first solution of step (a) to attain a temperature of 2°C to room temperature;

c) optionally adding a secondary non-aqueous solvent to the first solution of step (b) under constant stirring for 5 minutes to 10 minutes to obtain a second solution;

d) adding peptide drug to the second solution of step (c) and allowing to disperse to obtain a solution;

e) optionally filtering the solution of step (d) one or more times to obtain a clear solution; and

f) filling the clear solution of step (e) in suitable containers to obtain a composition in a ready-to-use form.

In an embodiment, in the process for the preparation of the injectable composition of the peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the said peptide drug is as described above in one or more embodiments of the invention.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises 100% primary non-aqueous solvent; or in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent can be used in a ratio ranging from about 99:1 to about 50:50.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises 100% primary non-aqueous solvent.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-

aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent can be used in a ratio ranging from about 99:1 to about 50:50.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent can be used in the ratio of 99:1, 95:5, 90:10, 85:15, 80:20, 70:30, 60:40 or 50:50.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent(s) can be used in the ratio of 90:10.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-aqueous solvent system, the primary non-aqueous solvent and the secondary non-aqueous co-solvent(s) can be used in the ratio of 85:15.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the primary non-aqueous solvent contained in the non-aqueous solvent system is selected from the group consisting of but not limited to ethylene glycol, propylene glycol, dipropylene glycol, tripropylene glycol, glycerol and polyethylene glycol or a mixture thereof.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the primary non-aqueous solvent is propylene glycol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the secondary non-aqueous co-solvent(s) is a (C_1-C_3)alkyl alcohol selected from the group consisting of but not limited to methanol, ethanol, absolute alcohol, 1-propanol and isopropanol (isopropyl alcohol) or a mixture thereof.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the

secondary non-aqueous co-solvent is isopropyl alcohol; ethanol or absolute alcohol; or a combination thereof.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the secondary non-aqueous co-solvent is ethanol.

In another embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the secondary non-aqueous co-solvent is absolute alcohol.

In another embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the secondary non-aqueous co-solvent is isopropyl alcohol.

In another embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the secondary non-aqueous co-solvent is a combination of ethanol/absolute alcohol and isopropyl alcohol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the polyol is selected from a group consisting of but not limited to glycerin, sucrose, lactose, glucose, fructose, arabinose, xylose, ribose, mannose, galactose, dextrose, sorbose, sorbitol, mannitol, maltose, cellobiose, xylitol, trehalose or a combination thereof.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the polyol is in the range of about 0.01% to about 10% of the total injectable composition of peptide drug.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the polyol is sorbitol or racemic salts or isomers thereof.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the polyol is D-sorbitol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises 100% propylene glycol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises propylene glycol and ethanol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises propylene glycol and absolute alcohol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises propylene glycol and isopropyl alcohol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises 100% propylene glycol; or in the non-aqueous solvent system, the propylene glycol and ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in a ratio ranging from about 99:1 to about 50:50.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the non-aqueous solvent system comprises 100% propylene glycol.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-aqueous solvent system, the propylene glycol and ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in the ratio ranging from about 99:1 to about 50:50.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-aqueous solvent system, propylene glycol and ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in the ratio of 99:1, 95:5, 90:10, 85:15, 80:20, 70:30, 60:40 or 50:50.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-

aqueous solvent system, propylene glycol and ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in the ratio of 90:10.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in the non-aqueous solvent system, propylene glycol and ethanol/absolute alcohol (and/or isopropyl alcohol) can be used in the ratio of 85:15.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the pH adjusting agent is selected from pharmaceutically acceptable acids, bases, or buffering agents.

In another embodiment, the pH of the ready-to-use peptide drug injectable composition obtained by the process as described above is between about 2.0 and about 11.0.

In another embodiment, the pH of the ready-to-use peptide drug injectable composition obtained by the process as described above is between about 4.0 and about 8.0

In another embodiment, the pH of the ready-to-use peptide drug injectable composition obtained by the process as described above is between about 4.0 and about 5.5.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the antioxidant is selected from but not limited to butylated hydroxytoluene, sodium metabisulphite acetylcysteine, ascorbyl palmitate, butylated hydroxyanisole, monothioglycerol, potassium nitrate, ascorbic acid or sodium ascorbate, sodium formaldehyde sulfoxylate, sodium bisulfite, vitamin E or a derivative thereof, propyl gallate, edetate, diethylenetriaminepentaacetic acid, triglycollamate, DL- or D-α-tocopherol, DL- or D-α-tocopheryl acetate, amino acids, stereoisomers of amino acids; or a combination thereof.

In an embodiment, in the process for the preparation of the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; the antioxidant is selected from butylated hydroxytoluene or sodium metabisulphite.

Method of use of the injectable composition:

In an aspect, the present invention relates to use of a stable, non-aqueous and ready-to-use composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; for the manufacture of a medicament for treating or preventing one or more diseases, conditions or disorders; wherein the said injectable composition is as described in one or more embodiments of the present invention as described herein above.

In an aspect, the present invention relates to a method of treating or preventing one or more diseases, conditions or disorders comprising administering to a subject in need thereof; a therapeutically effective amount of a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said injectable composition is as described in one or more embodiments of the present invention as described herein above.

In an embodiment, the diseases, disorders or conditions for the treatment or prevention of which the injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; of the present invention can be used, include, but are not limited to, metabolic disorders, autoimmune disorders, cardiovascular diseases, respiratory diseases, thyroid diseases, hormonal diseases, neurodegenerative diseases, bacterial infections, viral infections, fungal infections, renal diseases, hepatobiliary diseases, venereal diseases, platelet aggregation, inflammatory diseases, cancers, transplantation complications due to rejection reactions, graft rejection and hepatic diseases.

In another embodiment, the stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; can be packaged in a suitable container depending upon the composition and the method of administration of the composition. Suitable containers known to a person skilled in the art include vials, ampoules and infusion bag.

In another embodiment, the present invention provides a pharmaceutical kit comprising the stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said composition comprises of the peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; a non-aqueous solvent system consisting of a primary non-aqueous

solvent and optionally one or more secondary non-aqueous co-solvent(s); optionally a polyol; optionally a pH adjusting agent and optionally an antioxidant. The kit may further comprise a package insert, including information about the indication, usage, doses, direction for administration, contraindications, precautions and warnings. The kit may further contain optional materials for storing and/or administering the drug, for example an infusion bag as well as instructions for storage and use.

In another embodiment, the stable, non-aqueous and ready-to-use injectable composition of a peptide drug of the present invention; can be delivered to the subject intravenously. Methods of delivering the RTU injectable composition intravenously are well known in the art.

In another embodiment, the stable, non-aqueous and ready-to-use injectable composition of a peptide drug of the present invention; can be delivered to the subject by infusion. For example, the injectable dosage form may be delivered intravenously through infusion.

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within scope of the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not to limit the scope of the present invention

Examples

Example 1:

The injectable composition of daptomycin (RTU)

Ingredients	**mg/mL**
Daptomycin	50
Propylene Glycol	988
Ethanol	39.45
D-Sorbitol	0.1093
Sodium Hydroxide	q.s. (quantity sufficient)

Procedure:

a) Propylene glycol was taken in a glass bottle / stainless steel (SS) container.

b) Sodium hydroxide was dissolved in propylene glycol of step (a) to obtain a first solution by stirring for 60 minutes and attaining temperature of 2°C to 8°C.

c) Sorbitol was dissolved in ethanol to obtain a second solution.

d) The second solution obtained in step (c) was added to first solution obtained in step (b).

e) Daptomycin was then added to the solution obtained in step (d) to obtain a solution.

f) The solution obtained in step (e) was subject to turbulence for 30- 120 minutes to obtain a clear solution.

g) The clear liquid concentrate obtained in step (f) was filled in siliconised / non-siliconised vial and stoppered with Teflon coated rubber stoppers with nitrogen headspace to obtain a composition in a ready-to-use form.

Example 2:

The injectable composition of daptomycin (RTU)

Ingredients	**mg/mL**
Daptomycin	50
Propylene Glycol	988
Ethanol	39.45
D-Sorbitol	0.1093

Procedure:

a) Propylene glycol was taken in a glass bottle / stainless steel (SS) container.

b) Sodium hydroxide was dissolved in propylene glycol of step (a) to obtain a first solution by stirring for 60 minutes and attaining temperature of 2°C to 8°C.

c) Sorbitol was dissolved in ethanol to obtain a second solution.

d) The second solution obtained in step (c) was added to first solution obtained in step (b).

e) Daptomycin was then added to the solution obtained in step (d) to obtain a solution.

f) The solution obtained in step (e) was subjected to turbulence for 30- 120 minutes to obtain a clear solution.

g) The clear liquid concentrate obtained in step (f) was filled in siliconised/ non-siliconised vial and stoppered with Teflon coated rubber stoppers with nitrogen headspace to obtain a composition in a ready-to-use form.

Stability Studies (Example 2):

		Storage conditions					
		2-8°C		15°C		25°C / 60% RH	
Parameters	Initial	1M	2M	1M	2M	1M	2M
Assay	97.9	96.0	97.6	90.6	90.1	82.5	74.0

M - Months

Results of the stability studies performed for ready to use injectable Daptomycin composition mentioned according to Example 2 demonstrates that 1.9% degradation occurred at 2-8°C after one month stability whereas the composition was stable without degradation after 2 months. The composition is stable at 2-8°C.

Example 3:

The injectable composition of daptomycin (RTU)

Ingredients	**mg/mL**
Daptomycin	50
Propylene Glycol	988
Ethanol	39.45
D-Sorbitol	0.1093
Butylated hydroxytoluene	0.02

Procedure:

a) Propylene glycol was taken in a glass bottle / SS container.

b) Sorbitol and butylated hydroxytoluene were dissolved in ethanol to obtain a solution.

c) The solution thus obtained in step (b) was added to propylene glycol of step (a) with continuous stirring until complete miscibility was observed.

d) Daptomycin was then added to the solution obtained in step (c) to obtain a solution.

e) The solution obtained in step (d) was subjected to turbulence for 30-120 minutes to obtain a clear solution.

f) The clear liquid concentrate obtained in step (e) was filled in siliconised/ non-siliconised vial and stoppered with Teflon coated rubber stoppers with nitrogen headspace to obtain a composition in a ready-to-use form.

Stability Studies (Example 3):

		Storage conditions		
		2-8°C	15°C	25°C / 60% RH
Parameters	Initial	1M	1M	1M
Assay	102.7	100.9	97.1	88.7

M - Months

Results of the stability studies performed for ready to use injectable Daptomycin composition mentioned according to Example 3 demonstrates that the composition exhibited stability upto 1 month at 2-8°C.

Example 4:

The injectable composition of daptomycin (RTU)

Ingredients	**mg/mL**
Daptomycin	50
Propylene Glycol	988
Ethanol	39.45
D-Sorbitol	0.1093
Sodium Metabisulphite	0.50

Procedure:

a) Propylene glycol was taken in a glass bottle / SS container.

b) Sorbitol and sodium metabisulphite were dissolved in ethanol to obtain a solution.

c) The solution thus obtained in step (b) was added to propylene glycol of step (a) with continuous stirring until complete miscibility was observed.

d) Daptomycin was then added to the solution obtained in step (c) to obtain a solution.

e) The solution obtained in step (d) was subjected to turbulence for 30- 120 minutes to obtain a clear solution.

f) The clear liquid concentrate obtained in step (e) was filled in siliconised/ non-siliconised vial and stoppered with Teflon coated rubber stoppers with nitrogen headspace to obtain a composition in a ready-to-use form.

Stability Studies (Example 4):

		Storage conditions		
		2-8°C	15°C	25°C / 60% RH
Parameters	Initial	1M	1M	1M
Assay	103.9	99.5	92.8	91.6

M - Months

Results of the stability studies performed for ready to use injectable Daptomycin composition mentioned according to Example 4 demonstrates that the composition exhibited stability upto 1 month at 2-8°C.

We Claim:

1. A stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof comprising:
   (i) a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; wherein the said peptide drug is other than bivalirudin;
   (ii) a non-aqueous solvent system;
   (iii) optionally a polyol;
   (iv) optionally a pH adjusting agent; and
   (v) optionally an antioxidant.

2. The injectable composition according to claim 1, wherein the peptide drug is selected from daptomycin, nesiritide, cetrorelix acetate; or a combination thereof.

3. The injectable composition according to claim 1, wherein the non-aqueous solvent system comprises of a primary non-aqueous solvent.

4. The injectable composition according to claim 1, wherein the non-aqueous solvent system comprises of a primary non-aqueous solvent and one or more secondary non-aqueous co-solvents.

5. The injectable composition according to claim 1, wherein the non- aqueous solvent system comprises one or more solvent selected from the group consisting of ethylene glycol, propylene glycol, dipropylene glycol, tripropylene glycol, glycerol, polyethylene glycol, methanol, ethanol, absolute alcohol, 1-propanol and isopropanol (isopropyl alcohol) or a mixture thereof.

6. The injectable composition according to claim 3 or claim 4, wherein the primary non-aqueous solvent contained in the non-aqueous solvent system is selected from the group consisting of ethylene glycol, propylene glycol, dipropylene glycol, tripropylene glycol, glycerol and polyethylene glycol or a mixture thereof.

7. The injectable composition according to claim 4, wherein the secondary non-aqueous co-solvent contained in the non-aqueous solvent system is a (C_1-C_3)alkyl

alcohol selected from the group consisting of but not limited to methanol, ethanol, absolute alcohol, 1-propanol and isopropanol (isopropyl alcohol) or a mixture thereof.

8. The injectable composition according to claim 1, wherein the polyol is selected from a group consisting of glycerin, sucrose, lactose, glucose, fructose, arabinose, xylose, ribose, mannose, galactose, dextrose, sorbose, sorbitol, mannitol, maltose, cellobiose, xylitol, trehalose or a combination thereof.

9. The injectable composition according to claim 1, wherein the pH adjusting agent is selected from pharmaceutically acceptable acids, bases, or buffering agents.

10. The injectable composition according to claim 1, wherein the antioxidant is selected from butylated hydroxytoluene, sodium metabisulphite acetylcysteine, ascorbyl palmitate, butylated hydroxyanisole, monothioglycerol, potassium nitrate, ascorbic acid or sodium ascorbate, sodium formaldehyde sulfoxylate, sodium bisulfite, vitamin E or a derivative thereof, propyl gallate, edetate, diethylenetriaminepentaacetic acid, triglycollamate, DL- or D-α-tocopherol, DL- or D-α-tocopheryl acetate, amino acids, stereoisomers of amino acids; or a combination thereof.

11. The injectable composition according to claim 1, wherein the said composition contains the said peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; in a concentration in the range of 1 mg/mL to 200 mg/mL.

12. The injectable composition according to claim 4, wherein the said injectable composition comprises the primary non-aqueous solvent and the secondary non-aqueous co-solvent in the ratio ranging from 99:1 to 50:50.

13. The injectable composition according to claim 1, wherein the polyol is in the range of about 0.01% to about 10% of the total injectable composition of the peptide drug.

14. The injectable composition according to claim 1, wherein the pH is between about 2.0 and about 11.0.

15. The injectable composition according to claim 1, wherein the antioxidant is added in an amount preferably from 0.001 to 1% w/v.

16. A process for the preparation of a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof; comprising the steps of:
a) dissolving a pH adjusting agent in a non-aqueous solvent system consisting of a primary non-aqueous solvent to obtain a first solution;
b) optionally adding polyol and antioxidant to the secondary non-aqueous solvent under constant stirring until the polyol dissolves to obtain a second solution;
c) adding the first solution of step (a) to the second solution of step (b) under constant stirring to obtain a third solution;
d) dispersing the peptide drug in the third solution of step (c) to obtain a solution;
e) optionally filtering the solution of step (d) to obtain a clear solution; and
f) filling the clear solution of step (e) into a container to obtain a preparation in a ready-to-use form.

17. A process for the preparation of a stable, non-aqueous and ready-to-use injectable composition of a peptide drug or a pharmaceutically acceptable salt or a co-crystal thereof comprising the steps of:
a) dissolving polyol, optionally antioxidant and pH adjusting agent in secondary non-aqueous solvent to obtain a first solution;
b) adding primary non-aqueous solvent to the first solution of step (a) to obtain a second solution;
c) adding peptide drug to the second solution of step (b) and allowing to disperse to produce a solution;
d) optionally filtering the solution of step (c) one or more times to obtain a clear solution; and
e) filling the clear solution of step (d) into a container to obtain a composition in a ready-to-use form.

INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER

A61K 38/08 (2006.01) ***A61K 38/12 (2006.01)*** ***A61K 38/49 (2006.01)*** ***A61P 9/04 (2006.01)*** ***A61P 31/00 (2006.01)*** ***A61P 35/00 (2006.01)*** ***A61K 9/08 (2006.01)***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PATENTSCOPE: FP: (PIRAMAL ENTERPRISES), Sonavaria, Upadhyay, injectable and non-aqueous

ESPACE, AUSPAT and PAMS NOSE (internal) : PIRAMAL ENTERPRISES, Sonavaria and Upadhyay

INTESS (internal) : PIRAMAL ENTERPRISES, Sonavaria, Upadhyay and TEXT: Injectable, injection, non-aqueous and solvent

EPOQUE (Medline, EPODOC and WPIAP databases) and STN (Medline, CA Plus and Embase): (i) PIRAMAL ENTERPRISES, Sonavaria , Upadhyay, aqueous, solvent, ethanol, glycol, polar, pvp, injectable & similar terms ; (ii) Daptomycin, cubicin, urokinase, caspofungin, cancidas, fosaprepitant, bivalirudin, solvent, ethylene glycol, propylene glycol, ethanol and similar terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 January 2016	19 January 2016
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Grant McNeice AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832617

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/IB2015/057926**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/0230441 A1 (SOPPIMATH, K. et al.) 22 September 2011 paragraphs 0010, 0011, 0014, 0016, 0019, 0032 and 0039, Tables 1 and 5 and claim 1	1, 3-12 and 14-16
X	US 2012/0172808 A1 (SOPPIMATH, K. et al.) 05 July 2012 paragraphs 0010, 0011, 0014, 0015, 0017, 0019, 0032 and 0043, Tables 1 and 5 and claim 1	1, 3-12 and 14-16
X	WO 2007/084460 A2 (QUEST PHARMACEUTICAL SERVICES) 26 July 2007 paragraphs 0003, 0007, 0014, 0017, 0019, 0037, 0068, 00116, 00132 and 0139 and claims 1, 4, 19, 23 and 24	1 and 3-17
X	WO 2008/008363 A1 (QUEST PHARMACEUTICAL SERVICES , LLC.) 17 January 2008 pages 7, 9, 11, 12, 20, 21 (lines 2-7), 22, 26 and 27 and claims 1 and 16	1, 3-6, 9, 11, 12, 14, 16 and 17

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2015/057926**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
US 2011/0230441 A1	22 September 2011	US 2011230441 A1	22 Sep 2011
		US 9061037 B2	23 Jun 2015
		AU 2011227083 A1	04 Oct 2012
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Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2015/057926**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
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End of Annex

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