

[0011] An additional discovery by the inventors is that it is possible to prepare stable solutions of a therapeutic agent(s) solubilized in non-aqueous aprotic polar solvents (e.g. DMSO), by adding a specific amount of a compound, or combination of compounds, that function as an ionization stabilizing excipient. Without wishing to be bound by theory, it is believed that the ionization stabilizing excipient can act as a proton source (e.g., a molecule that can donate a proton to the therapeutic molecule) in the aprotic polar solvent system that may protonate the ionogenic groups on the therapeutic molecule such that the therapeutic molecule possesses an ionization profile having an improved physical and chemical stability in the aprotic polar solvent system. In one aspect of the present invention there is disclosed a stable formulation for parenteral injection. Alternatively, transdermal delivery such as through topical application to skin can be used.

[0011a] In one aspect of the present invention there is disclosed a stable glucagon formulation comprising: (a) a glucagon peptide or salt thereof, wherein the glucagon peptide or salt thereof is not been prepared by drying in the presence of a non-volatile buffer having a pH of 2 to 4; (b) an ionization stabilizing excipient, wherein the ionization stabilizing excipient is a mineral acid; and (c) an aprotic polar solvent; wherein (i) the glucagon peptide or salt thereof is dissolved in the aprotic solvent in an amount from about 0.1 mg/mL up to the solubility limit of the glucagon peptide or salt thereof, and (ii) the ionization stabilizing excipient is dissolved in the aprotic solvent in an amount to stabilize the ionization of the glucagon peptide or salt thereof.

[0011b] In another aspect of the present invention there is disclosed a use of a formulation as described herein in the manufacture of a medicament for treating hypoglycemia.

[0011c] In another aspect of the present invention there is disclosed a method of stably formulating a glucagon peptide comprising the steps of: (a) determining an appropriate ionization profile for the glucagon peptide or a salt thereof in an aprotic polar solvent system; (b) mixing at least one ionization stabilizing excipient with the aprotic solvent to impart the appropriate concentration of the at least one ionization stabilizing excipient to establish the ionization profile determined in step (a); and (c) dissolving the glucagon peptide or salt thereof in the aprotic solvent having an appropriate ionization stabilizing excipient concentration to physically and chemically stabilize the glucagon peptide or salt thereof for at least one year at room temperature.

[0012] Certain embodiments are directed to a formulation of a therapeutic agent comprising a therapeutic agent at a concentration of at least, at most, or about 0.1, 1, 10, 50, or 100 mg/mL to 150, 200, 300, 400, or 500 mg/ml or up to the solubility limit of the therapeutic agent in the aprotic polar solvent system comprising a concentration of at least one ionization stabilizing excipient that provides physical and chemical stability to the therapeutic agent. In certain aspects the therapeutic agent is a peptide. In further aspects the therapeutic agent is a small molecule. The formulation can comprise an ionization stabilizing excipient at a concentration of at least, at most, or about 0.01, 0.1, 0.5, 1, 10, or 50 mM to 10, 50, 75, 100, 500, 1000 mM, or up to the solubility limit of the ionization stabilizing excipient in the aprotic polar solvent system. In certain aspects the ionization stabilizing excipient concentration is between 0.1 mM to 100 mM. In certain embodiments the ionization stabilizing excipient may be a suitable mineral acid, such as hydrochloric acid. In certain aspects the ionization stabilizing excipient may be an organic acid, such as an amino acid, amino acid derivative, or the salt of an amino acid or amino acid derivative (examples include glycine, trimethylglycine (betaine), glycine hydrochloride, and trimethylglycine (betaine) hydrochloride). In a further aspect the amino acid can be glycine or the amino acid derivative trimethylglycine. In certain aspects a peptide is less than 150, 100, 75, 50, or 25 amino acids. In further aspects the aprotic solvent system comprises DMSO. The aprotic solvent can be deoxygenated, e.g., deoxygenated DMSO. In certain embodiments the formulation may be prepared by first adding the ionization stabilizing excipient to the aprotic polar solvent system, followed by addition of the therapeutic molecule. Alternatively, the

CLAIMS

1. A stable glucagon formulation comprising:
 - (a) a glucagon peptide or salt thereof, wherein the glucagon peptide or salt thereof is not been prepared by drying in the presence of a non-volatile buffer having a pH of 2 to 4;
 - (b) an ionization stabilizing excipient, wherein the ionization stabilizing excipient is a mineral acid; and
 - (c) an aprotic polar solvent;wherein (i) the glucagon peptide or salt thereof is dissolved in the aprotic solvent in an amount from about 0.1 mg/mL up to the solubility limit of the glucagon peptide or salt thereof, and (ii) the ionization stabilizing excipient is dissolved in the aprotic solvent in an amount to stabilize the ionization of the glucagon peptide or salt thereof.
2. The formulation of claim 1, wherein the ionization stabilizing excipient is at a concentration of 0.1 mM to less than 100 mM.
3. The formulation of claim 1, wherein the mineral acid is selected from hydrochloric acid, sulfuric acid, or nitric acid.
4. The formulation of claim 1, wherein the aprotic solvent is DMSO.
5. The formulation of claim 1, wherein the aprotic solvent is a deoxygenated aprotic solvent.
6. The formulation of claim 5, wherein the deoxygenated aprotic solvent is deoxygenated DMSO.
7. The formulation of claim 1, wherein the ionization stabilizing excipient is sulfuric acid and the aprotic solvent is DMSO.
8. The formulation of claim 1, wherein the moisture content is less than 10, 5, or 3 %.

9. The formulation of claim 1, further comprising a preservative at less than 10, 5, or 3% w/v.
10. The formulation of claim 9, wherein the preservative is benzyl alcohol.
11. The formulation of claim 1, further comprising a disaccharide at less than 10, 5, or 3% w/v.
12. The formulation of claim 11, wherein the disaccharide is trehalose.
13. Use of a formulation of claim 1 in the manufacture of a medicament for treating hypoglycemia.
14. The use of claim 13, wherein the medicament is to be administered by parenteral injection.
15. The use of claim 14, wherein the injection is intracutaneous injection.
16. A method of stably formulating a glucagon peptide comprising the steps of:
 - (a) determining an appropriate ionization profile for the glucagon peptide or a salt thereof in an aprotic polar solvent system;
 - (b) mixing at least one ionization stabilizing excipient with the aprotic solvent to impart the appropriate concentration of the at least one ionization stabilizing excipient to establish the ionization profile determined in step (a); and
 - (c) dissolving the glucagon peptide or salt thereof in the aprotic solvent having an appropriate ionization stabilizing excipient concentration to physically and chemically stabilize the glucagon peptide or salt thereof for at least one year at room temperature.
17. The method of claim 16, wherein the ionization stabilizing excipient is hydrochloric acid, nitric acid, sulfuric acid, or a combination thereof.

18. The method of claim 16, wherein the ionization stabilizing excipient concentration is between 0.1 mM to 100 mM.
19. The method of claim 16, wherein the aprotic solvent is DMSO.