POLYPEPTIDE FORMULATIONS

BACKGROUND

[0001] Polypeptide therapeutics play an important role in medicine. Many current therapeutics include polypeptides such as enzymes and antibodies. A typical route of administration for polypeptide therapeutics is intravenous or subcutaneous injection. Injection of therapeutic agents is associated with well-known drawbacks. For many years, researchers have sought alternative compositions and methods for administration of polypeptide therapeutics.

SUMMARY

[0002] The present disclosure provides, among other things, methods and compositions for the administration (e.g., oral administration) of polypeptides. Many polypeptides are typically formulated as liquid solutions for administration by intravenous or subcutaneous injection. The present disclosure provides, among other things, encapsulated polypeptide formulations and suspensions for oral delivery that include an amorphous polypeptide composition or a crystallized polypeptide composition (e.g., a powder form that includes amorphous polypeptide or crystallized polypeptide) and a pharmaceutically acceptable carrier including a vitamin E agent. The present disclosure includes the surprising discovery that oral delivery of formulations disclosed herein that include a polypeptide and Vitamin E successfully deliver polypeptides to the bloodstream. Without wishing to be bound by any particular scientific theory, the present disclosure further includes the surprising discovery that polypeptides orally administered in a formulation as disclosed herein including a vitamin E agent are efficiently delivered to the bloodstream, lymphatic system, and thoracic duct. In various examples, polypeptides orally administered in a formulation as disclosed herein including a vitamin E agent are efficiently delivered to the bloodstream via the lymphatic system, e.g., at least in part via the thoracic duct. The present disclosure includes the realization that formulations provided herein that include polypeptide and vitamin E provide platform are of broad utility with a generalized ability to delivery polypeptides to the bloodstream. Accordingly, those of skill in the art will appreciate from the present disclosure, including the present Examples, that formulations provided herein are advantageous and useful without need to specify the polypeptide included therein. Further still, the present disclosure demonstrates

unexpectedly advantageous characteristics of various oral delivery of formulations disclosed herein, including improved pharmacokinetic properties such as rate of delivery into the bloodstream and/or increased half-life.

[0003] In at least one aspect, the present disclosure includes a polypeptide formulation for oral delivery including (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier including a vitamin E agent, optionally where (i) the polypeptide formulation is an encapsulated polypeptide formulation including a core and a pharmaceutically acceptable capsule, where the core includes the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation.

[0004] In at least one example, the present disclosure includes a method of delivering a polypeptide to the bloodstream of a subject, the method including orally administering to the subject a polypeptide formulation including (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier including a vitamin E agent, optionally where (i) the polypeptide formulation is an encapsulated polypeptide formulation including a core and a pharmaceutically acceptable capsule, where the core includes the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation. In certain examples, the polypeptide is delivered to the bloodstream via the lymphatic system, optionally where the polypeptide is delivered to the blood stream via the thoracic duct. In another aspect of the present disclosure, there is provided a use of (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier comprising a vitamin E agent in the manufacture of a polypeptide formulation for delivering a polypeptide to the bloodstream of a subject, wherein the polypeptide formulation is to be orally administered to the subject, optionally wherein (i) the polypeptide formulation is an encapsulated polypeptide formulation comprising a core and a pharmaceutically acceptable capsule, wherein the core comprises the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation, optionally wherein the polypeptide is delivered to the bloodstream via the lymphatic system, optionally wherein the polypeptide is delivered to the bloodstream via the thoracic duct.

[0005] In at least one example, the present disclosure includes a method of delivering a polypeptide to the thoracic duct or lymph of a subject, the method including orally administering to the subject a polypeptide formulation including (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier including a vitamin E agent,

optionally where (i) the polypeptide formulation is an encapsulated polypeptide formulation including a core and a pharmaceutically acceptable capsule, where the core includes the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation. In a further aspect of the present disclosure, there is provided a use of (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier comprising a vitamin E agent in the manufacture of a polypeptide formulation for delivering a polypeptide to the thoracic duct or lymph of a subject, wherein the polypeptide formulation is to be orally administered to the subject, optionally wherein (i) the polypeptide formulation is an encapsulated polypeptide formulation comprising a core and a pharmaceutically acceptable capsule, wherein the core comprises the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation.

[0005a] In another aspect of the present disclosure, there is provided a polypeptide formulation as disclosed herein for use in therapy.

[0006] In at least one aspect, the present disclosure includes a method of producing an encapsulated polypeptide formulation for oral delivery, the method including encapsulating within a capsule a core including (i) an amorphous polypeptide composition or a crystallized polypeptide composition and (ii) a pharmaceutically acceptable carrier including a vitamin E agent. In at least one aspect, the present disclosure includes a method of producing a polypeptide suspension for oral delivery,

the method including suspending (i) a crystallized polypeptide composition or an amorphous polypeptide composition in (ii) a pharmaceutically acceptable carrier including a vitamin E agent.

[0007] In certain examples, the polypeptide includes: (i) a therapeutic polypeptide; (ii) an antibody agent or fragment thereof; (iii) a monoclonal antibody or fragment thereof; (iv) a fusion polypeptide; (v) an immunoglobulin; (vi) an enzyme; or (vii) an analog and/or modified form of any of (i)-(vi), optionally where the polypeptide is modified by one or more of pegylation, acetylation, amidation, lipidation, methylation, phosphorylation, glycosylation, glycation, sulfation, mannosylation, nitrosylation, acylation, palmitoylation, prenylation, fatty acids, or a combinations thereof. In certain examples, the polypeptide is selected from an antibody (e.g., an anti-HER2 antibody, e.g., trastuzumab), a GLP-1 receptor agonist, human glucagon-like peptide-1(GLP-1) or an analog thereof (e.g., a synthetic analog, e.g., liraglutide), parathyroid hormone (e.g., recombinant human parathyroid hormone analog, e.g., teriparatide), insulin (e.g., Humulin®), rituximab, bevacizumab, cetuximab, etanercept, infliximab, agalsidase beta, agalsidase alfa, imiglucerase, aliglucerase alfa, velaglucerase alfa, alglucerase, sebelipase alpha, laronidase, idursulfase, elosulfase alpha, galsulfase, pancrelipase, sapropterin, eliglustat, galsulfase, asfotase alfa, pegvaliase, elapegademase, sacrosidase, Factor I, Factor II, Factor III, Factor IV, Factor V, Factor VI, Factor VII, Factor VIII, Factor IX, Factor X, Factor XI, Factor XII, Factor XIII, von Willebrand factor, etanercept, aflibercept, rilonacept, alefacept, romiplostim, abatacept/belatacept, and/or denileukin-diftitox, or an analog or derivative thereof, optionally where the polypeptide is natural, synthetic, or engineered. In certain examples, the polypeptide has a molecular weight between about 50 Da and 25 kDa, optionally where the molecular weight is between about 50 Da and about 1 kDa, about 50 Da and about 2 kDa, about 50 Da and about 3 kDa, about 50 Da and about 4 kDa, about 50 Da and about 5 kDa, about 50 Da and about 10 kDa, about 50 Da and about 15 kDa, or about 50 Da and about 20 kDa. In certain examples, the polypeptide has a molecular weight between about 25 kDa and about 1,000 kDa, optionally where the molecular weight is between about 25 kDa and about 500 kDa, about 100 kDa and about 500 kDa, about 120 kDa and about 250 kDa, or about 150 kDa and about 300 kDa. In certain examples, the polypeptide formulation includes about 1 μg to about 2,000 mg of the polypeptide, optionally where the polypeptide formulation includes about 1 μg to about 1,000 mg, about 1 μg to about 500 mg, about 1 μg to about 400 mg, about 1 μg to about 300 mg, about 1 μg to about 200 mg, about 1 μg to about 100 mg, about 1 μg to about 50 mg, about 1 μg to about 25 mg, about 1 μg to about 20 mg, about 1 μg to about 15 mg, about 1 μg to about 10 mg, about 1 μg to about 5 mg, about 1 μg to about 1 mg, about 1 μg to about 500 μg, about 1 μg to about 250 μg, about 1 μg to about 200 μg, about 1 μg to about 150 μg, about 1 μg to about 100 μg, about 1 μg to about 50 μg, about 1 mg to about 1,000 mg, about 1 mg to about 500 mg, about 1 mg to about 400 mg, about 1 mg to about

300 mg, about 1 mg to about 200 mg, about 1 mg to about 100 mg, about 1 mg, to about 50 mg, about 1 mg to about 25 mg of the polypeptide.

[0008] In certain examples, the polypeptide formulation includes about 1 mg to about 2,000 mg of a vitamin E agent, optionally where the polypeptide formulation includes about 1 mg to about 1,000 mg, about 1 mg to about 500 mg, about 1 mg to about 400 mg, about 1 mg to about 300 mg, about 1 mg to about 200 mg, about 1 mg to about 100 mg, about 1 mg to about 50mg, or about 1 mg to about 25 mg of a vitamin E agent. In certain examples, the polypeptide formulation includes a molar excess or excess by weight of a vitamin E agent relative to the amount of polypeptide in the polypeptide formulation, optionally where in the excess is a fold excess of at least 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 500, or 1,000 fold.

[0009] In certain examples, the crystallized polypeptide composition includes crystals of polypeptide having an average particle size of less than 25 microns, e.g., less than 20, 15, 10, 5, 4, 3, 2, 1, or 0.5 microns, optionally where the crystals of polypeptide have an average particle size that is between 0.5 microns and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns or where the crystals of polypeptide have an average particle size that is between 1 micron and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns. In certain examples, the amorphous polypeptide composition includes particles of polypeptide having an average particle size of less than 25 microns, e.g., less than 20, 15, 10, 5, 4, 3, 2, 1, or 0.5 microns, optionally where the particles of polypeptide have an average particle size that is between 0.5 microns and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns or where the particles of polypeptide have an average particle size that is between 1 micron and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns.

[0010] In certain examples, the polypeptide composition includes lyophilized polypeptide. In certain examples, the polypeptide composition includes microcrystals of polypeptide. In certain examples, the polypeptide composition includes a powder including crystallized polypeptide.

[0011] In certain examples, the core is a viscous solution. In certain examples, the capsule is a hard-shell capsule or soft-shell capsule, optionally where the capsule is a gelatin capsule or HPMC capsule. In certain examples, the capsule is formulated for delivery to the gut, optionally where the capsule is formulated for delivery to stomach and/or intestine. In certain examples, the capsule includes an enteric coating.

[0012] In certain examples, the core further includes one or more excipients or additives selected from the group consisting of aggregation-reducing agents, sugars or sugar alcohols, polysaccharides, stabilizers, hyaluronidase, buffering agents, preservatives, carriers, antioxidants, chelating agents, natural or synthetic polymers, cryoprotectants, lyoprotectants, surfactants, bulking agents, acidifying agents, ingredients to reduce injection site discomfort, antifoaming agents, alkalizing agents, vehicles, aggregation inhibitors, solubilizing agents, tonicity modifiers, and stabilizing agents and

combinations thereof. In certain examples, the one or more excipients or additives are individually or cumulatively present at a concentration between 0.1 mM and about 1,000 mM, between about 0.1 mM and about 500 mM, between about 0.1 mM and about 200 mM. or between about 0.1 mM and about 100 mM._In certain examples, (i) the aggregation-reducing agent(s)s are selected from the group consisting of nicotinic acid, caffeine citrate, caffeine nicotinate, caffeine, octyl- β-D-glucopyranoside, and n-dodecyl-β-D-maltoside and optionally in combination with one or more of arginine, tryptophan, histidine, proline, cysteine, methionine, β-alanine, Potassium Glutamate, Arginine Ethylester, lysine, aspartic acid, glutamic acid, glycine, DTPA (diethylenetriaminepentaacetic acid), EGTA(aminopolycarboxylic acid), EDTA (Ethylenediaminetetraacetic acid), hydroxy propyl beta (HP-Beta) cyclodextrins, hydroxy propyl gamma (HP-Gamma) cyclodextrins, sulfo-butyl ether (SBE) cyclodextrins, TMAO (trimethylamine N-oxide), trehalose, ethylene glycol, betaine, xylitol, sorbitol, 6-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)hexanoic acid (NBD-X), methyl acetyl phosphate (MAP), citraconic anhydride, pyrophosphate, citrate, and combinations thereof; (ii) the tonicity modifier(s) are selected from the group consisting of arginine, cysteine, histidine, glycine, sodium chloride, potassium chloride, sodium citrate, saccharides such as sucrose, glucose, dextrose, glycerin or mannitol, and combinations thereof; (iii) the antioxidant(s) are selected from the group consisting of glycine, lysine, EDTA, DTPA, sorbitol, mannitol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sufur dioxide, tocopherol, and combinations thereof; or (iv) the lyoprotectant(s) are selected from the group consisting of sucrose, lactose, trehalose, dextran, erythritol, arabitol, xylitol, sorbitol, maltose, lactulose, maltulose, glucitol, maltitol, lactitol, isomaltulose and mannitol; amino acids, such as arginine or histidine or proline or glycine; lyotropic salts, such as magnesium sulfate; propylene glycol, glycerol, poly(ethylene glycol), or poly(propylene glycol); gelatin, dextrins, modified starch, carboxymethyl cellulose, and combinations thereof.

DEFINITIONS

[0013] ***A, An, The*:** As used herein, “a”, “an”, and “the” refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” discloses embodiments of exactly one element and embodiments including more than one element.

[0014] ***About**:* As used herein, term “about”, when used in reference to a value, refers to a value that is similar, in context to the referenced value. In general, those skilled in the art,

CLAIMS

What is claimed is:

1. A polypeptide formulation for oral delivery comprising (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier comprising a vitamin E agent,

optionally wherein (i) the polypeptide formulation is an encapsulated polypeptide formulation comprising a core and a pharmaceutically acceptable capsule, wherein the core comprises the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation.

2. Use of (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier comprising a vitamin E agent in the manufacture of a polypeptide formulation for delivering a polypeptide to the bloodstream of a subject, wherein the polypeptide formulation is to be orally administered to the subject,

optionally wherein (i) the polypeptide formulation is an encapsulated polypeptide formulation comprising a core and a pharmaceutically acceptable capsule, wherein the core comprises the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation,

optionally wherein the polypeptide is delivered to the bloodstream via the lymphatic system, optionally wherein the polypeptide is delivered to the bloodstream via the thoracic duct.

3. Use of (i) a crystallized polypeptide composition or an amorphous polypeptide composition and (ii) a pharmaceutically acceptable carrier comprising a vitamin E agent in the manufacture of a polypeptide formulation for delivering a polypeptide to the thoracic duct or lymph of a subject, wherein the polypeptide formulation is to be orally administered to the subject,

optionally wherein (i) the polypeptide formulation is an encapsulated polypeptide formulation comprising a core and a pharmaceutically acceptable capsule, wherein the core

comprises the crystallized polypeptide composition or amorphous polypeptide composition and the pharmaceutically acceptable carrier or (ii) the polypeptide formulation is a suspension formulation.

4. A method of producing an encapsulated polypeptide formulation for oral delivery, the method comprising encapsulating within a capsule a core comprising (i) an amorphous polypeptide composition or a crystallized polypeptide composition and (ii) a pharmaceutically acceptable carrier comprising a vitamin E agent.

5. A method of producing a polypeptide suspension for oral delivery, the method comprising suspending (i) a crystallized polypeptide composition or an amorphous polypeptide composition in (ii) a pharmaceutically acceptable carrier comprising a vitamin E agent.

6. The polypeptide formulation of claim 1, or use of claims 2 or 3, or method of claim 4 or 5, wherein the polypeptide comprises:

(i) a therapeutic polypeptide;

(ii) an antibody agent or fragment thereof;

(iii) a monoclonal antibody or fragment thereof;

(iv) a fusion polypeptide;

(v) an immunoglobulin;

(vi) an enzyme; or

(vii) an analog and/or modified form of any of (i)-(vi), optionally wherein the polypeptide is modified by one or more of pegylation, acetylation, amidation, lipidation, methylation, phosphorylation, glycosylation, glycation, sulfation, mannosylation, nitrosylation, acylation, palmitoylation, prenylation, fatty acids, or a combinations thereof, optionally wherein:

(a) the polypeptide is selected from an antibody (e.g., an anti-HER2 antibody, e.g., trastuzumab), a GLP-1 receptor agonist, human glucagon-like peptide-1(GLP-1) or an analog thereof (e.g., a synthetic analog, e.g., liraglutide), parathyroid hormone (e.g., recombinant human parathyroid hormone analog, e.g., teriparatide), insulin (e.g., Humulin®), rituximab, bevacizumab, cetuximab, etanercept, infliximab, agalsidase beta, agalsidase alfa, imiglucerase,

aliglucerase alfa, velaglucerase alfa, alglucerase, sebelipase alpha, laronidase, idursulfase, elosulfase alpha, galsulfase, pancrelipase, sapropterin, eliglustat, galsulfase, asfotase alfa, pegvaliase, elapegademase, sacrosidase, Factor I, Factor II, Factor III, Factor IV, Factor V, Factor VI, Factor VII, Factor VIII, Factor IX, Factor X, Factor XI, Factor XII, Factor XIII, von Willebrand factor, etanercept, aflibercept, rilonacept, alefacept, romiplostim, abatacept/belatacept, and/or denileukin-diftitox, or an analog or derivative thereof, optionally wherein the polypeptide is natural, synthetic, or engineered, and/or

(b) the polypeptide has a molecular weight between about 50 Da and 25 kDa, optionally wherein the molecular weight is between about 50 Da and about 1 kDa, about 50 Da and about 2 kDa, about 50 Da and about 3 kDa, about 50 Da and about 4 kDa, about 50 Da and about 5 kDa, about 50 Da and about 10 kDa, about 50 Da and about 15 kDa, or about 50 Da and about 20 kDa,

or wherein the polypeptide has a molecular weight between about 25 kDa and about 1,000 kDa, optionally wherein the molecular weight is between about 25 kDa and about 500 kDa, about 100 kDa and about 500 kDa, about 120 kDa and about 250 kDa, or about 150 kDa and about 300 kDa, and/or

(c) the polypeptide formulation comprises about 1 µg to about 2,000 mg of the polypeptide, optionally wherein the polypeptide formulation comprises about 1 µg to about 1,000 mg, about 1 µg to about 500 mg, about 1 µg to about 400 mg, about 1 µg to about 300 mg, about 1 µg to about 200 mg, about 1 µg to about 100 mg, about 1 µg to about 50 mg, about 1 µg to about 25 mg, about 1 µg to about 20 mg, about 1 µg to about 15 mg, about 1 µg to about 10 mg, about 1 µg to about 5 mg, about 1 µg to about 1 mg, about 1 µg to about 500 µg, about 1 µg to about 250 µg, about 1 µg to about 200 µg, about 1 µg to about 150 µg, about 1 µg to about 100 µg, about 1 µg to about 50 µg, about 1 mg to about 1,000 mg, about 1 mg to about 500 mg, about 1 mg to about 400 mg, about 1 mg to about 300 mg, about 1 mg to about 200 mg, about 1 mg to about 100 mg, about 1 mg, to about 50 mg, about 1 mg to about 25 mg of the polypeptide, and/or

(d) wherein the polypeptide formulation comprises about 1 mg to about 2,000 mg of a vitamin E agent, optionally wherein the polypeptide formulation comprises about 1 mg to about 1,000 mg,

about 1 mg to about 500 mg, about 1 mg to about 400 mg, about 1 mg to about 300 mg, about 1 mg to about 200 mg, about 1 mg to about 100 mg, about 1 mg to about 50mg, or about 1 mg to about 25 mg of a vitamin E agent, and/or

(e) wherein the polypeptide formulation comprises a molar excess or excess by weight of a vitamin E agent relative to the amount of polypeptide in the polypeptide formulation, optionally where in the excess is a fold excess of at least 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 500, or 1,000 fold.

7. The polypeptide formulation of claim 1 or 6, or use of any one of claims 2-3 or 6, or method of any one of claims 4-6, wherein the crystallized polypeptide composition comprises crystals of polypeptide having an average particle size of less than 25 microns, e.g., less than 20, 15, 10, 5, 4, 3, 2, 1, or 0.5 microns, optionally wherein the crystals of polypeptide have an average particle size that is between 0.5 microns and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns or wherein the crystals of polypeptide have an average particle size that is between 1 micron and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns.

8. The polypeptide formulation of claim 1 or 6-7, or use of any one of claims 2-3 or 6-7, or method of any one of claims 4-7, wherein the amorphous polypeptide composition comprises particles of polypeptide having an average particle size of less than 25 microns, e.g., less than 20, 15, 10, 5, 4, 3, 2, 1, or 0.5 microns, optionally wherein the particles of polypeptide have an average particle size that is between 0.5 microns and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns or wherein the particles of polypeptide have an average particle size that is between 1 micron and 1, 2, 3, 4, 5, 10, 15, 20, or 25 microns.

9. The polypeptide formulation of claim 1 or 6-8, or use of any one of claims 2-3 or 7-8, or method of any one of claims 4-8, wherein:
(a) the polypeptide composition comprises lyophilized polypeptide, and/or
(b) the polypeptide composition comprises microcrystals of polypeptide, and/or
(c) the polypeptide composition comprises a powder comprising crystallized polypeptide.

10. The polypeptide formulation of claim 1 or 6-9, or use of any one of claims 2-3 or 7-9, or method of any one of claims 4-9, wherein the core is a viscous solution.

11. The polypeptide formulation of claim 1 or 6-10, or use of any one of claims 2-3 or 7-10, or method of any one of claims 4-10, wherein:
(a) the capsule is a hard-shell capsule or soft-shell capsule, optionally wherein the capsule is a gelatin capsule or HPMC capsule, and/or
(b) the capsule is formulated for delivery to the gut, optionally wherein the capsule is formulated for delivery to stomach and/or intestine.

12. The polypeptide formulation of claim 1 or 6-11, or use of any one of claims 2-3 or 7-11, or method of any one of claims 4-11, wherein the capsule comprises an enteric coating.

13. The polypeptide formulation of claim 1 or 6-12, or use of any one of claims 2-3 or 7-12, or method of any one of claims 4-12, wherein the core further comprises one or more excipients or additives selected from the group consisting of aggregation-reducing agents, sugars or sugar alcohols, polysaccharides, stabilizers, hyaluronidase, buffering agents, preservatives, carriers, antioxidants, chelating agents, natural or synthetic polymers, cryoprotectants, lyoprotectants, surfactants, bulking agents, acidifying agents, ingredients to reduce injection site discomfort, antifoaming agents, alkalizing agents, vehicles, aggregation inhibitors, solubilizing agents, tonicity modifiers, and stabilizing agents and combinations thereof,

optionally wherein the one or more excipients or additives are individually or cumulatively present at a concentration between 0.1 mM and about 1,000 mM, between about 0.1 mM and about 500 mM, between about 0.1 mM and about 200 mM. or between about 0.1 mM and about 100 mM.

14. The polypeptide formulation, use, or method of claim 13, wherein:

(i) the aggregation-reducing agent(s)s are selected from the group consisting of nicotinic acid, caffeine citrate, caffeine nicotinate, caffeine, octyl- β-D-glucopyranoside, and n-dodecyl-β-D-maltoside and optionally in combination with one or more of arginine, tryptophan, histidine, proline, cysteine, methionine, β-alanine, Potassium Glutamate, Arginine Ethylester, lysine,

aspartic acid, glutamic acid, glycine, DTPA (diethylenetriaminepentaacetic acid), EGTA(aminopolycarboxylic acid), EDTA (Ethylenediaminetetraacetic acid), hydroxy propyl beta (HP-Beta) cyclodextrins, hydroxy propyl gamma (HP-Gamma) cyclodextrins, sulfo-butyl ether (SBE) cyclodextrins, TMAO (trimethylamine N-oxide), trehalose, ethylene glycol, betaine, xylitol, sorbitol, 6-(N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)hexanoic acid (NBD-X), methyl acetyl phosphate (MAP), citraconic anhydride, pyrophosphate, citrate, and combinations thereof;

(ii) the tonicity modifier(s) are selected from the group consisting of arginine, cysteine, histidine, glycine, sodium chloride, potassium chloride, sodium citrate, saccharides such as sucrose, glucose, dextrose, glycerin or mannitol, and combinations thereof;

(iii) the antioxidant(s) are selected from the group consisting of glycine, lysine, EDTA, DTPA, sorbitol, mannitol, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, propyl gallate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sufur dioxide, tocopherol, and combinations thereof; or

(iv) the lyoprotectant(s) are selected from the group consisting of sucrose, lactose, trehalose, dextran, erythritol, arabitol, xylitol, sorbitol, maltose, lactulose, maltulose, glucitol, maltitol, lactitol, isomaltulose and mannitol; amino acids, such as arginine or histidine or proline or glycine; lyotropic salts, such as magnesium sulfate; propylene glycol, glycerol, poly(ethylene glycol), or poly(propylene glycol); gelatin, dextrins, modified starch, carboxymethyl cellulose, and combinations thereof.

15. A polypeptide formulation of any one of claims 1 or 6 to 14 for use in therapy.