syringe, pen, reservoir for a pump or a closed loop system. Also provided herein is a syringe or vial containing any of the compositions provided herein.

The compositions provided herein containing an insulin, such as a regular insulin or a rapid acting insulin analog (e.g. aspart, lispro or glulisine or other insulin analog), can be used in methods and uses for treating diabetes. For example, provided herein are methods of treating diabetes by administering to a subject a therapeutically effective amount of a any of the above stable composition provided herein. The diabetes to be treated includes type 1 diabetes mellitus, type 2 diabetes mellitus or gestational diabetes. Also provided herein are methods for controlling blood glucose levels in a subject by administering to a subject a therapeutically effective amount of a stable composition provided herein containing a fast-acting insulin. In practicing the methods herein, the stable compositions are administered subcutaneously or intraperitoneally, for example, via a syringe or insulin pen or by continuous subcutaneous infusion. In practicing the methods herein, the stable compositions can be administered prior to a meal as prandial insulin therapy. In the methods provided herein, the stable compositions can be administered using a delivery method to achieve continuous subcutaneous insulin infusion, such as via an insulin pump or a closed loop system. In some instances, the methods provided herein include administering another anti-diabetic drug, that is selected from among, but not limited to, sulfonylureas, biguanides, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, peptide analogs, including glucagon-like peptide (GLP) analogs and, gastric inhibitory peptide (GIP) analogs and DPP-4 inhibitors.

In one aspect, there is provided a composition, comprising:
a hyaluronidase; and
lysyl lysine (Lys-Lys) in an amount to render the hyaluronidase stable.

In one aspect, there is provided a syringe or vial, comprising the stable composition as described herein.

In one aspect, there is provided a closed loop system, comprising the stable composition as described herein.

In one aspect, there is provided an insulin pump, comprising the stable composition as described herein.

In one aspect, there is provided an insulin pen, comprising the stable composition as described herein.

In one aspect, there is provided the use of the composition as described herein for treating diabetes or for controlling blood glucose levels in a subject.

In one aspect, there is provided the use of the composition as described herein for the manufacture of a medicament for treating diabetes or for controlling blood glucose levels in a subject.

DETAILED DESCRIPTION

A. Definitions

B. HYALURONAN DEGRADING ENZYME FORMULATIONS AND GENERATING INSULIN CO-FORMULATIONS

1. Hyaluronan-Degrading Enzyme Formulations
2. Fast-Acting Insulin Formulations
3. Hyaluronan-Degrading Enzyme and Insulin Co-formulations
   - a. Opposing requirements for stability
     - i. Preservatives
     - ii. NaCl and pH
   - b. Compatible Co-Formulation

C. HYALURONAN DEGRADING ENZYMES

1. Hyaluronidases
   - a. Mammalian-type hyaluronidases
     PH20
   - b. Bacterial hyaluronidases
   - c. Hyaluronidases from leeches, other parasites and crustaceans

WHAT IS CLAIMED:

1. A stable co-formulation composition, wherein:

the composition has a pH of between or about between 6.8 to 7.8; and

the composition comprises:

a therapeutically effective amount of a fast-acting insulin;

a hyaluronan-degrading enzyme in an amount sufficient to render the composition super-fast acting;

NaCl at a concentration between or about between 50 mM to 200 mM;

an anti-microbially effective amount of a preservative or mixture of preservatives; and

a stabilizing agent or agents,

whereby the composition is stable for at least 6 months at a temperature from or from about 2°C to 8°C and/or for at least 14 days at a temperature from or from about 20°C to 30°C.

2. The stable co-formulation of claim 1, wherein:

the hyaluronan-degrading enzyme in the co-formulation retains at least 50% of the initial hyaluronidase activity for at least 6 months at a temperature from or from about 2°C to 8°C and/or for at least 14 days at a temperature from or from about 20°C to 30°C; and/or

the insulin in the composition retains:

at least 90% potency or recovery of the initial level of insulin in the composition for at least 6 months at a temperature from or from about 2°C to 8°C and/or for at least 14 days at a temperature from or from about 20°C to 30°C; and/or

at least 90% of the initial insulin purity for at least 6 months at a temperature from or from about 2°C to 8°C and/or for at least 14 days at a temperature from or from about 20°C to 30°C; and/or

less than 2% high molecular weight (HMWt) insulin species for at least 6 months at a temperature from or from about 2°C to 8°C and/or for at least 14 days at a temperature from or from about 20°C to 30°C.

3. The stable co-formulation of claim 1 or claim 2, wherein the NaCl concentration is between or about between 80 mM to 200 mM, 80 mM to 140 mM, 50

mM to 100 mM, 80 mM to 100 mM, 50 mM to 80 mM, 100 mM to 140 mM or 120 mM to 140 mM.

4. The stable co-formulation of any of claims 1-3, comprising a sufficient amount of a buffering agent to maintain the pH range of between or about between 6.8 to 7.8.

5. A stable co-formulation composition, wherein:

the composition has a pH of between or about between 6.5 to 7.5;

the composition comprises:

a therapeutically effective amount of a fast-acting insulin;

a hyaluronan-degrading enzyme in an amount sufficient to render the composition super-fast acting;

NaCl at a concentration between or about between 120 mM to 200 mM;

an anti-microbially effective amount of a preservative or mixture of preservatives; and

a stabilizing agent or agents; and

whereby the composition is stable for at least 3 days at a temperature from or from about 32°C to 40°C and/or is stable for at least 3 hours under agitation.

6. The stable co-formulation of claim 5, wherein the stabilizing agent comprises an effective amount of a hyaluronidase inhibitor.

7. The stable co-formulation of claim 6, wherein the hyaluronidase inhibitor is selected from among a protein, a substrate of a hyaluronan-degrading enzyme, polysaccharides, fatty acids, lanostanoids, antibiotics, anti-nematodes, synthetic organic compounds and a plant-derived bioactive component.

8. The stable co-formulation of claim 6 or claim 7, wherein the hyaluronidase inhibitor is selected from among a glycosaminoglycan (GAG), serum hyaluronidase inhibitor, *Withania somnifera* glycoprotein (WSG), heparin, heparin sulfate, dermatan sulfate, chitosans, β-(1,4)-galacto-oligosaccharides, sulphated verbascose, sulphated planteose, pectin, poly(styrene-4-sulfonate), dextran sulfate, sodium alginate, polysaccharide from *Undaria pinnatifida*, mandelic acid condensation polymer, eicosatrienoic acid, nervonic acid, oleanolic acid, aristolochic acid, ajmaline, reserpine, flavone, desmethoxycentauredine, quercetin, apigenin,

kaempferol, silybin, luteolin, luteolin-7-glucoside, phloretin, apiin, hesperidin, sulphonated hesperidin, calycosin-7-O-β-D-glucopyranoside, sodium flavone-7-sulphate, flavone 7-fluoro-4'-hydroxyflavone, 4'-chloro-4,6-dimethoxychalcone, sodium 5-hydroxyflavone 7-sulphate, myricetin, rutin, morin, glycyrrhizin, vitamin C, D-isoascorbic acid, D-saccharic 1,4-lactone, L-ascorbic acid-6-hexadecanoate (Vcpal), 6-O-acylated vitamin C, catechin, nordihydroguaiaretic acid, curcumin, N-propyl gallate, tannic acid, ellagic acid, gallic acid, phlorofucofuroeckol A, dieckol, 8,8'-bieckol, procyanidine, gossypol, celecoxib, nimesulide, dexamethasone, indomethcin, fenoprofen, phenylbutazone, oxyphenbutazone, salysylates, disodium cromoglycate, sodium aurothiomalate, transilist, traxanox, ivermectin, linocomycin and spectinomycin, sulfamethoxazole and trimerthoprim, neomycin sulphate, 3α-acetylpolyporenic acid A, (25S)-(+)-12α-hydroxy-3α-methylcarboxyacetate-24-methyllanosta-8,24(31)-diene-26-oic acid, lanostanoid, polyporenic acid c, PS53 (hydroquinone-sulfonic acid-formaldehyde polymer), polymer of poly (styrene-4-sulfonate), VERSA-TL 502, 1-tetradecane sulfonic acid, mandelic acid condensation polymer (SAMMA), 1,3-diacetylbenzimidazole-2-thione, N-monoacylated benzimidazol-2thione, N,N'-diacylated benzimidazol-2-thione, alkyl-2-phenylindole derivate, 3-propanoylbenzoxazole-2-thione, N-alkylated indole derivative, N-acylated indole derivate, benzothiazole derivative, N-substituted indole-2- and 3-carboxamide derivative, halogenated analogs (chloro and fluoro) of N-substituted indole-2- and 3-carboxamide derivative, 2-(4-hydroxyphenyl)-3-phenylindole, indole carboxamides, indole acetamides, 3-benzolyl-1-methyl-4-phenyl-4-piperidinol, benzoyl phenyl benzoate derivative, L-arginine derivative, guanidium HCL, L-NAME, HCN, linamarin, amygdalin, hederagenin, aescin, CIS-hinokiresinol and 1,3-di-p-hydroxyphenyl-4-penten-1-one.

9. The stable co-formulation of any of claims 6-8, wherein the hyaluronidase inhibitor is a hyaluronidase substrate that is a hyaluronan (HA) oligosaccharide.

10. The stable co-formulation of claim 9, wherein the concentration of HA is between or about between 1 mg/mL to 20 mg/mL.

11. The stable co-formulation of any of claims 5-10, wherein:

the hyaluronan-degrading enzyme in the co-formulation retains at least 50% of the initial hyaluronidase activity for at least 3 days at a temperature from or from about 32°C to 40°C or is stable for at least 3 days under agitation; and

the insulin in the composition retains:

at least 90% potency or recovery of the initial level of insulin in the composition for at least 3 days at a temperature from or from about 32°C to 40°C or is stable for at least 3 days under agitation; and/or

at least 90% of the initial insulin purity for at least 3 days at a temperature from or from about 32°C to 40°C or is stable for at least 3 hours under agitation; and/or

less than 2% high molecular weight (HMWt) insulin species for at least 3 days at a temperature from or from about 32°C to 40°C or is stable for at least 3 days under agitation.

12. The stable co-formulation of any of claims 5-11, wherein the NaCl concentration is between or about between 150 mM to 200 mM or 160 mM to 180 mM.

13. The stable co-formulation of any of claims 5-12, comprising a sufficient amount of a buffering agent to maintain the pH range of between or about between 6.5 to 7.5.

14. The stable co-formulation of any of claims 1-13, wherein the hyaluronan-degrading enzyme is a hyaluronidase or a chondroitinase.

15. The stable co-formulation of any of claims 1-14, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is active at neutral pH.

16. The stable co-formulation of any of claims 1-15, wherein:

the hyaluronan-degrading enzyme lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronan-degrading enzyme contains C-terminal truncations of one or more amino acid residues to remove all or part of a GPI anchor.

17. The stable co-formulation of any of claims 1-16, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is a PH20 or a C-terminal truncated form thereof.

18. The stable co-formulation of any of claims 1-17, wherein the hyaluronan-degrading enzyme is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273

19. The stable co-formulation of any of claims 1-18, wherein the hyaluronan-degrading enzyme is a C-terminal truncated PH20 that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 4-9.

20. The stable co-formulation of any of claims 1-19, wherein the amount of a hyaluronan-degrading enzyme is between or about between 10 U/mL to 20000 U/mL, 10 U/mL to 15000 U/mL, 10 U/mL to 10000 U/mL, 10 U/mL to 5000 U/mL, 50 U/mL to 10000 U/mL, 50 U/mL to 4000 U/mL, 100 U/mL to 2000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 2000 U/mL, or 100 U/mL to 1000 U/mL.

21. The stable co-formulation of any of claims 1-20, wherein the amount of a hyaluronan-degrading enzyme is at least or is about or is 30 U/mL, 35 U/mL, 40 U/mL, 50 U/mL, 100 U/mL, 150 U/mL, 200 U/mL, 250 U/mL, 300 U/mL, 350 U/mL, 400 U/mL, 450 U/mL, 500 U/mL, 600 U/mL, 700 U/mL, 800 U/mL, 900 U/mL, 1000 U/mL, 2000 U/mL, 3000 U/mL, 4000 U/mL, 5000 U/mL, 10000 U/mL, 15000 U/mL or 20000 U/mL.

22. The stable co-formulation of any of claims 1-21, wherein the fast-acting insulin is a regular insulin.

23. The stable co-formulation of claim 22, wherein the regular insulin is a human insulin or pig insulin.

24. The stable co-formulation of claim 22 or claim 23, wherein the regular insulin is an insulin with an A chain having a sequence of amino acids set forth in SEQ ID NO:103 and a B chain having a sequence of amino acids set forth in SEQ ID NO:104; or an insulin with an A chain having a sequence of amino acids set forth as amino acid residue positions 88-108 of SEQ ID NO:123 and a B chain having a sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

25. The stable co-formulation of any of claims 1-21, wherein the fast-acting insulin is an insulin analog.

26. The stable co-formulation of any of claims 1-25, wherein the fast-acting insulin is an insulin analog selected from among insulin lispro, insulin aspart and insulin glulisine.

27. The stable co-formulation of claim 25 or claim 26, wherein the insulin analog is selected from among an insulin having an A chain with a sequence of amino acids set forth in SEQ NOS:103 and a B chain having a sequence of amino acids set forth in any of SEQ NOS:147-149.

28. The stable co-formulation of any of claims 1-27, wherein the amount of fast-acting insulin is 10 U/mL to 1000 U/mL, 50 U/mL to 500 U/mL, 100 U/mL to 1000 U/mL or 500 U/mL to 1000 U/mL, inclusive.

29. The stable co-formulation of any of claims 4 and 13-28, wherein the buffering agent is selected from among Tris, histidine, phosphate and citrate.

30. The stable co-formulation of any of claims 4 and 13-29, wherein the buffering agent is Tris.

31. The stable co-formulation of any of claims 4 and 13-30, wherein the concentration of the buffering agent is between or is between about 1 mM to 100 mM, 10 mM to 50 mM or 20 mM to 40 mM.

32. The stable co-formulation of any of claims 1-31, wherein the preservative(s) in the formulation comprises one or more of a phenolic preservative(s), a non-phenolic preservative(s) or a phenolic preservative(s) and a non-phenolic preservative(s).

33. The stable co-formulation of any of claims 1-32, wherein the preservative(s) is(are) selected from among phenol, m-cresol, methylparaben, benzyl alcohol, thimerosal, benzalkonium chloride, 4-chloro-1-butanol, chlorhexidine dihydrochloride, chlorhexidine digluconate, L-phenylalanine, EDTA, bronopol, phenylmercuric acetate, glycerol, imidurea, chlorhexidine, sodium dehydroacetate, o-cresol, p-cresol, chlorocresol, cetrimide, benzethonium chloride, ethyl paraben, propylparaben, butylparaben and any combinations thereof.

34. The stable co-formulation of any of claims 1-33, wherein the formulation contains a single preservative or a mixture of preservatives that contains 2, 3 or 4 different preservatives.

35. The stable co-formulation of any of claims 1-34, comprising at least one phenolic preservative.

36. The stable co-formulation of any of claims 1-35, wherein the preservative(s) is(are) phenol, m-cresol or phenol and m-cresol.

37. The stable co-formulation of any of claims 1-36, wherein the total amount of the one or more preservative agents as a percentage (%) of mass concentration (w/v) in the formulation is or is between 0.1% and 0.4%, 0.1% to 0.3%, 0.15% to 0.325%, 0.15% to 0.25%, 0.1% to 0.2%, 0.2%to 0.3% or 0.3% to 0.4% inclusive.

38. The stable co-formulation of any of claims 1-37, wherein the preservatives are phenol and m-cresol and the amount as a % of mass concentration (w/v) in the formulation is between or about between 0.1% to 0.25% phenol and between or about between 0.05% to 0.2% m-cresol, is between or about between 0.10% to 0.2% phenol and between or about between 0.6% to 01.8% m-cresol, between or about between 0.1% to 0.15% phenol and 0.8% t 0.15% m-cresol, is between or about between 0.10% to 0.15% phenol and between or about between 0.06 to 0.09% m-cresol or is between or about between 0.12% to 0.18% phenol and between or about between 0.14 to 0.22% m-cresol.

39. The stable co-formulation of any of claims 1-38, comprising a stabilizing agent that is selected from among an amino acid, an amino acid derivative, an amine, a sugar, a polyols, a salt and a surfactant.

40. The stable co-formulation of claim 39, wherein the stabilizing agent is an amino acid that is glycine or proline.

41. The stable co-formulation of claim 39 or claim 40, wherein the concentration of the amino acid is between or between about 0.01 M to 1 M, 0.01 M to 0.1 M, 0.1M to 0.75M or 0.2M to 0.5M, inclusive.

42. The stable co-formulation of claim 39, wherein the stabilizing agent is an amino acid is selected from among arginine, glutamic acid, and/or salts thereof and/or combinations thereof.

43. The stable co-formulation of claim 42, wherein the concentration of the amino acids are 1 to 100 mM, 10 to 100 mM, or of or of about 30 mM, 50 mM or 80 mM.

44. The stable co-formulation of any of claims 1-43, wherein the stabilizing agent is a surfactant and the amount of surfactant as a % of mass concentration (w/v) in the formulation is between or about between 0.005% to 1.0%, 0.01% to 0.5%, 0.01% to 0.1%, 0.01% to 0.05%, or 0.01% to 0.02%.

45. The stable co-formulation of claim 44, wherein the surfactant is selected from among a polypropylene glycol, polyethylene glycol, glycerin, sorbitol, poloxamer and polysorbate.

46. The stable co-formulation of claim 44 or claim 45, wherein the surfactant is selected from among poloxamer 188, polysorbate 20 and polysorbate 80.

47. The stable co-formulations of any of claims 1-46, wherein:

the stabilizing agent is a surfactant that is poloxamer 188 and is provided in an amount as a % of mass concentration (w/v) of between or about between 0.01% to 0.05%; or

the stabilizing agent is a surfactant that is polysorbate 20 and is provided in an amount as a % of mass concentration (w/v) of between or about between 0.01% to 0.05%; or

the stabilizing agent is a surfactant that is polysorbate 80 and is provided in an amount as a % of mass concentration (w/v) of between or about between 0.01% to 0.05%.

48. The stable co-formulations of any of claims 1-47, comprising a tonicity modifier to maintain the osmolarity of between or about between 245 mOsm/kg to 305 mOsm/kg.

49. The stable co-formulation of claim 48, wherein the tonicity modifier is selected from among glycerin, salt, amino acids, polyalcohols and trehalose.

50. The stable co-formulation of claim 48 or claim 49, comprising glycerin in a concentration less than 60 mM, less than 55 mM, less than 50 mM, less than 45 mM, less than 40 mM, less than 35 mM, less than 30 mM, less than 25 mM, less than 20 mM, less than 15 mM, less than 10 mM.

51. The stable co-formulation of any of claims 48-50, wherein:

the fast-acting insulin is an insulin analog that is insulin aspart and the formulation comprises glycerin in a concentration between or about between 20 mM to 50 mM, inclusive; or

the fast acting insulin is a regular insulin or is insulin lispro and the formulation comprises glycerin in a concentration between or about between 40 mM to 60 mM, inclusive.

52. The stable co-formulation of any of claims 1-51, comprising an antioxidant.

53. The stable co-formulation of claim 52, wherein the antioxidant is selected from among cysteine, tryptophan and methionine.

54. The stable co-formulation of claim 52 or claim 53, wherein the antioxidant is at a concentration from between or from about between 5 mM to 50 mM, 5 mM to 40 mM, 5 mM to 20 mM or 10 mM to 20 mM, inclusive.

55. The stable co-formulation of claim 53, wherein the antioxidant is methionine and the concentration is between or about between 10 mM to 20 mM.

56. The stable co-formulation of any of claims 1-55, comprising zinc.

57. The stable co-formulation of claim 56, wherein the concentration of zinc is between or about between 0.001 to 0.1 mg per 100 units of insulin (mg/100U), 0.001 to 0.05 mg/100U or 0.01 to 0.05 mg/100U.

58. The stable co-formulation of any of claims 1-57, comprising a nicotinic compound.

59. The stable co-formulation of claim 58, wherein the nicotinic compound is selected from among nicotinamide, nicotinic acid, niacin, niacinamide, vitamin B3 and/or salts thereof and/or any combination thereof.

60. The stable co-formulation of claim 58 or claim 59, wherein the nicotinic compound(s) are present in a concentration from or from about 1 mm to 150 mM, 10 mM to 150 mM, 50 mM to 100 mM or of or of about 80 mM.

61. The stable co-formulation of any of claims 1-60, wherein the formulation has a pH of between or about between 7.0 to 7.6, and comprises:

a hyaluronan-degrading enzyme that is a PH20 in an amount between or about between 100 U/mL to 1000 U/mL, inclusive;

a fast-acting insulin analog in an amount between or about between 10 U/mL to 1000 U/mL, inclusive;

a Tris buffering agent at a concentration of between or about between 10 mM to 50 mM, inclusive;

NaCl at a concentration of between or about between 50 to 200 mM, inclusive;

methionine at a concentration between or about between 5 mM to 50 mM, inclusive;

glycerin at a concentration from between or about between 0 mM to 50 mM, inclusive;

a surfactant that is poloxamer 188, polysorbate 20 or polysorbate 80 at a percentage (%) of mass concentration (w/v) of between or about between 0.01% to 0.5%; and

a preservative(s) that comprises phenol at a percentage (%) of mass concentration (w/v) of between or between about between 0.1% to 0.25% and m-cresol at a % w/v of between or between about 0.05% to 0.2%.

62. The stable co-formulation of claim 61, comprising zinc at a concentration of 0.001 to 0.1 mg per 100 units of insulin (mg/100U).

63. The stable co-formulation of claim 61 or claim 62, wherein:

the fast-acting insulin is a fast-acting insulin analog that is insulin lispro,

the formulation has a pH between or about between 7.0 to 7.6; and

the formulation comprises:

a hyaluronan-degrading enzyme that is a PH20 in an amount between or about between 100 U/mL to 1000 U/mL, inclusive;

insulin lispro in an amount between or about between 10 U/mL to 1000 U/mL, inclusive;

a Tris buffering agent at a concentration of between or about between 25 mM to 35 mM, inclusive;

NaCl at a concentration of between or about between 50 mM to 120 mM, inclusive;

methionine at a concentration between or about between 10 mM to 30 mM, inclusive;

glycerin at a concentration from between or about between 40 mM to 60 mM, inclusive;

a surfactant that is poloxamer 188, polysorbate 20 or polysorbate 80 at a percentage (%) of mass concentration (w/v) of between or about between 0.01% to 0.05%, inclusive;

zinc at a concentration of 0.017 to 0.024 mg per 100 units of insulin (mg/100U); and

a preservative(s) that comprises a percentage (%) of mass concentration(w/v) of between or about between 0.08% to 0.17% phenol, inclusive, and between or about between 0.07% to 0.17% m-cresol.

64. The stable co-formulation of claim 63, wherein the NaCl concentration is between or about between 70 mM to 100 mM.

65. The stable co-formulation of claim 61 or claim 62, wherein:

the fast-acting insulin is a fast-acting insulin analog that is insulin aspart,

the formulation has a pH between or about between 7.0 to 7.6; and

the formulation comprises:

a hyaluronan-degrading enzyme that is a PH20 in an amount between or about between 100 U/mL to 1000 U/mL, inclusive;

insulin aspart in an amount between or about between 10 U/mL to 1000 U/mL, inclusive;

a Tris buffering agent at a concentration of between or about between 25 mM to 35 mM, inclusive;

NaCl at a concentration of between or about between 80 mM to 160 mM, inclusive;

methionine at a concentration between or about between 10 mM to 30 mM, inclusive;

glycerin at a concentration from between or about between 20 mM to 50 mM, inclusive;

a surfactant that is poloxamer 188, polysorbate 20 or polysorbate 80 at a percentage (%) of mass concentration (w/v) of between or about between 0.01% to 0.05%, inclusive;

zinc at a concentration of 0.017 to 0.024 mg per 100 units of insulin (mg/100U); and

a preservative(s) that comprises a percentage (%) of mass concentration(w/v) of between or about between 0.08% to 0.17% phenol, inclusive, and between or about between 0.07% to 0.17% m-cresol.

66. The stable co-formulation of claim 65, wherein the NaCl concentration is or is about between 70 mM to 100 mM.

67. The stable co-formulation of claim 61 or claim 62, wherein:

the fast-acting insulin is a fast-acting insulin analog that is insulin glulisine;

the formulation has a pH between or about between 7.0 to 7.6; and

the formulation comprises:

a hyaluronan-degrading enzyme that is a PH20 in an amount between or about between 100 U/mL to 1000 U/mL, inclusive;

insulin glulisine in an amount between or about between 10 U/mL to 1000 U/mL, inclusive;

a Tris buffering agent at a concentration of between or about between 25 mM to 35 mM, inclusive;

NaCl at a concentration of between or about between 80 mM to 200 mM, inclusive;

methionine at a concentration between or about between 10 mM to 30 mM, inclusive;

glycerin at a concentration from between or about between 40 mM to 60 mM, inclusive;

a surfactant that is poloxamer 188 at a percentage (%) of mass concentration (w/v) of between or about between 0.01% to 0.05%, inclusive; and

a preservative(s) that comprises a percentage (%) of mass concentration(w/v) of between or about between 0.08% to 0.17% phenol, inclusive, and between or about between 0.07% to 0.17% m-cresol.

68. The stable co-formulation of claim 67, wherein the NaCl concentration is between or about between 100 mM to 150 mM.

69. The stable co-formulation of any of claims 1-68 that is formulated for multi-dose administration.

70. A composition, comprising:

a therapeutically effective amount of a hyaluronan-degrading enzyme; and

lysyl lysine (Lys-Lys) in an amount to render the hyaluronan-degrading enzyme stable.

71. The composition of claim 70, wherein the amount of Lys-Lys is sufficient such that the hyaluronan-degrading enzyme retains at least 50% of the initial hyaluronidase activity for at least three (3) days at 37°C.

72. The composition of claim 70 or claim 71, wherein the hyaluronan-degrading enzyme retains at least 50% of the initial hyaluronidase activity at 37°C for at least 4 days, 5 days, 6 days, one week, two weeks, three weeks, one month, two months, three months, four months, five months, six months or more.

73. The composition of any of claims 70-72, wherein the hyaluronan-degrading enzyme retains at least 50% of the initial hyaluronidase activity for at least one month at 37°C.

74. The composition of any of claims 70-73 wherein the Lys-Lys concentration is between or about between 5 mM to 120 mM, 10 mM to 100 mM, 10 mM to 50 mM, 30 mM to 110 mM, 30 mM to 80 mM, 50 mM to 100 mM or 100 mM to 120 mM.

75. The composition of any of claims 70-74, wherein the pH of the formulation is between or about between 6.5 to 8.0, 6.5 to 7.4, 6.8 to 7.8, 7.0 to 7.6 or 6.8 to 7.2, inclusive.

76. The composition of any of claims 70-75, wherein the formulation further comprises a stabilizing agent.

77. The composition of claim 76, wherein the stabilizing agent is selected from among an amino acid, an amino acid derivative, an amine, a sugar, a polyol, a salt and a surfactant.

78. The composition of claim 76 or claim 77, wherein the stabilizing agent is a surfactant and the amount of surfactant, as a % of mass concentration (w/v) in the formulation, is between or about between 0.0005% to 1.0%, 0.0005% to 0.005%, 0.001% to 0.01%, 0.01% to 0.5%, 0.01% to 0.1%, 0.01% to 0.05%, or 0.01% to 0.02%, inclusive.

79. The composition of claim 77 or claim 78, wherein the surfactant is selected from among a polypropylene glycol, polyethylene glycol, glycerin, sorbitol, poloxamer and polysorbate.

80. The composition of any of claims 77-79, wherein the surfactant is selected from among poloxamer 188, polysorbate 20 and polysorbate 80.

81. The composition of any of claims 70-80, wherein the composition comprises an antioxidant.

82. The composition of claim 81, wherein the antioxidant is selected from among cysteine, tryptophan and methionine.

83. The composition of claim 82, wherein the antioxidant is methionine.

84. The composition of any of claims 81-83, wherein the antioxidant is at a concentration from between or from about between 5 mM to 50 mM, 5 mM to 40 mM, 5 mM to 20 mM or 10 mM to 20 mM, inclusive.

85. The composition of any of claims 70-84, comprising a tonicity modifier to maintain the osmolarity of between or about between 245 mOsm/kg to 500 mOsm/kg, inclusive.

86. The composition of claim 85, wherein the tonicity modifier is selected from among glycerin, salt, amino acids, polyalcohols and trehalose.

87. The composition of claim 85 or claim 86, wherein the tonicity modifier is a salt that is NaCl and the concentration of NaCl is or is about between 20 mM to 200 mM, 40 mM to 160 mM, 80 mM to 120 mM, 20 mM to 80 mM or 50 mM to 150 mM, inclusive.

88. The composition of any of claims 70-87, comprising NaCl at a concentration of less than 150 mM, less than 140 mM, less than 130 mM, less than 120 mM, less than 110 mM, less than 100 mM, less than 90 mM, less than 80 mM, less than 70 mM, less than 60 mM, less than 50 mM, less than 40 mM, less than 30 mM, less than 20 mM, less than 10 mM, or less.

89. The composition of any of claims 70-88, comprising a sufficient amount of a buffering agent to maintain the pH range of between or about between 6.5 to 8.0, 6.8 to 7.8, 7.0 to 7.6, 6.5 to 7.2, or 6.8 to 7.4, inclusive.

90. The composition of claim 89, wherein the buffering agent is selected from among Tris, histidine, phosphate and citrate.

91. The composition of claim 89 or claim 90, wherein the buffering agent is a phosphate that is sodium phosphate.

92. The composition of any of claims 89-91, wherein the concentration of the buffering agent is between or is between about 1 mM to 100 mM, 10 mM to 80 mM, 5 mM to 50 mM or 20 mM to 40 mM, inclusive.

93. The composition of any of claims 70-92, wherein the hyaluronan-degrading enzyme is a hyaluronidase or a chondroitinase.

94. The composition of any of claims 70-93, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is active at neutral pH.

95. The composition of any of claims 70-94, wherein:

the hyaluronan-degrading enzyme lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or

the hyaluronan-degrading contains C-terminal truncations of one or more amino acid residues to remove all or part of a GPI anchor.

96. The composition of any of claims 70-95, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is a PH20 or a C-terminally truncated fragment thereof.

97. The composition of any of claims 70-96, wherein the hyaluronan-degrading enzyme is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273.

98. The composition of any of claims 70-97, wherein the hyaluronan-degrading enzyme is a C-terminal truncated PH20 that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 4-9.

99. The composition of any of claims 70-98, wherein the amount of a hyaluronan-degrading enzyme is between or about between 10 U/mL to 20,000 U/mL, 50 U/mL to 15,000 U/mL, 50 U/mL to 10,000 U/mL, 50 U/mL to 5000 U/mL, 50 U/mL to 4000 U/mL, 100 U/mL to 10000 U/mL, 100 U/mL to 5000 U/mL, 100 U/mL to 2000 U/mL, 300 U/mL to 5000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL

to 5000 U/mL, 600 U/mL to 2000 U/mL, 100 U/mL to 1000 U/mL, 200 U/mL to 800 U/mL, 100 U/mL to 500 U/mL, or 150 U/mL to 300 U/ml, inclusive.

100. The composition of any of claims 70-99, wherein the concentration of Lys-Lys is 5 mM to 50 mM, inclusive.

101. The composition of any of claim 70-100, wherein:

the pH of the composition is between or about between 6.5 to 7.2;

and the composition comprises:

a hyaluronan-degrading enzyme in an amount that is between or about between 100 U/mL to 500 U/mL, inclusive;

Lys-Lys at a concentration that is between or about between 5 mM to 30 mM, inclusive;

NaCl at a concentration less than 140 mM NaCl;

a surfactant that is polysorbate 80 at a percentage (%) of mass concentration (w/v) of between or about between 0.01% to 0.05%, inclusive;

methionine at a concentration that is between or about between 5 mM to 20 mM, inclusive; and

sodium phosphate at a concentration that is between or about between 5 mM to 50 mM, inclusive.

102. The composition of any of claims 70-101, wherein the hyaluronan-degrading enzyme is a PH20 or a C-terminally truncated fragment thereof.

103. The composition of any of claims 70-102, further comprising a fast-acting insulin.

104. The composition of claim 103, wherein the concentration of Lys-Lys is 30 mM to 120 mM, 50 mM to 105 mM or 80 mM to 100 mM, inclusive.

105. The composition of claim 103 or claim 104, wherein the fast-acting insulin is a regular insulin.

106. The composition of claim 105, wherein the regular insulin is a human insulin or pig insulin.

107. The composition of claim 105 or claim 106, wherein the regular insulin is an insulin with an A chain having a sequence of amino acids set forth in SEQ ID NO:103 and a B chain having a sequence of amino acids set forth in SEQ ID NO:104; or an insulin with an A chain having a sequence of amino acids set forth as amino

acid residue positions 88-108 of SEQ ID NO:123 and a B chain having a sequence of amino acids set forth as amino acid residue positions 25-54 of SEQ ID NO:123.

108. The composition of any of claims 103-107, wherein the fast-acting insulin is an insulin analog.

109. The composition of claim 108, wherein the insulin analog is selected from among insulin aspart, insulin lispro and insulin glulisine.

110. The composition of claim 108 or claim 109, wherein the insulin analog is selected from among an insulin having an A chain with a sequence of amino acids set forth in SEQ NOS:103 and a B chain having a sequence of amino acids set forth in any of SEQ NOS:147-149.

111. The composition of any of claims 103-110, wherein the amount of fast-acting insulin is between or is about between 10 U/mL to 1000 U/mL, 20 U/mL to 500 U/mL, 50 U/mL to 300 U/mL or 200 U/mL to 800 U/mL, inclusive.

112. The composition of any of claims 103-111, wherein the fast-acting insulin is an insulin analog and the hyaluronan-degrading enzyme is a PH20 or a C-terminally truncated fragment thereof.

113. The composition of any of claims 103-112, wherein:

the fast-acting insulin is an insulin analog that is glulisine and the concentration of Lys-Lys is 50 to 105 mM; or

the fast-acting insulin is an insulin analog that is insulin aspart or insulin lispro and the concentration of Lys-Lys is 80 to 100 mM.

114. The composition of any of claims 70-113 that is for single dosage administration or is for multiple dosage administration.

115. The composition of claim 114, wherein the composition is for multiple dosage administration and comprises an anti-microbially effective amount of a preservative or mixture of preservatives.

116. The composition of claim 115, wherein the preservative(s) in the formulation comprises one or more of a phenolic preservative(s), a non-phenolic preservative(s) or a phenolic preservative(s) and a non-phenolic preservative(s).

117. The composition of claim 115 or claim 116, wherein the preservative(s) is(are) selected from among phenol, m-cresol, methylparaben, benzyl alcohol, thimerosal, benzalkonium chloride, 4-chloro-1-butanol, chlorhexidine

dihydrochloride, chlorhexidine digluconate, L-phenylalanine, EDTA, bronopol, phenylmercuric acetate, glycerol, imidurea, chlorhexidine, sodium dehydroacetate, o-cresol, p-cresol, chlorocresol, cetrimide, benzethonium chloride, ethyl paraben, propylparaben, butylparaben and any combinations thereof.

118. The composition of any of claims 115-117, wherein the formulation contains a single preservative; or

contains a mixture of preservatives that contains 2, 3 or 4 different preservatives.

119. The composition of any of claims 115-118, comprising at least one phenolic preservative.

120. The composition of any of claims 115-119, wherein the preservative(s) is(are) phenol, m-cresol or phenol and m-cresol.

121. The composition of any of claims 115-120, wherein the total amount of the one or more preservative agents as a percentage (%) of mass concentration (w/v) in the formulation is or is between 0.1% and 0.4%, 0.1% to 0.3%, 0.15% to 0.325%, 0.15% to 0.25%, 0.1% to 0.2%, 0.2% to 0.3% or 0.3% to 0.4%, inclusive.

122. The composition of any of claims 115-121, wherein the preservatives are phenol and m-cresol and the amount as a % of mass concentration (w/v) in the formulation is between or about between 0.1% to 0.25% phenol and between or about between 0.05% to 0.2% m-cresol, is between or about between 0.10% to 0.2% phenol and between or about between 0.06% to 0.18% m-cresol, is between or about between 0.1% to 0.15% phenol and 0.08% to 0.15% m-cresol, is between or about between 0.10% to 0.15% phenol and between or about between 0.06 to 0.09% m-cresol or is between or about between 0.12% to 0.18% phenol and between or about between 0.14 to 0.22% m-cresol, inclusive.

123. The composition of any of claims 70-122, wherein:

the pH of the composition is between or about between 6.8 to 7.4; and

the composition comprises:

a hyaluronan-degrading enzyme that is a PH20 in an amount between or about between 100 U/mL to 1000 U/mL, inclusive;

a fast-acting insulin analog that is insulin glulisine is an amount between or about between 10 U/mL to 1000 U/mL, inclusive;

Lys-Lys at a concentration between or about between 50 mM to 105 mM, inclusive;

NaCl at a concentration of less than 100 mM;

a surfactant that is polysorbate 20 at a percentage (%) of mass concentration (w/v) of between or about between 0.0005% to 0.005%, inclusive;

methionine at a concentration between or about between 5 mM to 20 mM, inclusive; and

a preservative(s) that comprises phenol at a percentage (%) of mass concentration (w/v) of between or between about between 0.1% to 0.25% and m-cresol at a % w/v of between or between about 0.05% to 0.2%.

124. The composition of any of claims 70-122, wherein:

the pH of the composition is between or about between 6.8 to 7.4; and

the composition comprises:

a hyaluronan-degrading enzyme that is a PH20 in an amount between or about between 100 U/mL to 1000 U/mL, inclusive;

a fast-acting insulin analog that is insulin aspart or insulin lispro is an amount between or about between 10 U/mL to 1000 U/mL, inclusive;

Lys-Lys at a concentration between or about between 80 mM to 100 mM, inclusive;

NaCl at a concentration of less than 30 mM;

a surfactant that is polysorbate 20 at a percentage (%) of mass concentration (w/v) of between or about between 0.0005% to 0.005%, inclusive;

methionine at a concentration between or about between 5 mM to 20 mM, inclusive; and

a preservative(s) that comprises phenol at a percentage (%) of mass concentration (w/v) of between or between about between 0.1% to 0.25% and m-cresol at a % w/v of between or between about 0.05% to 0.2%.

125. A composition, comprising:

a therapeutically effective amount of a hyaluronan-degrading enzyme; and

$MgCl_2$ in a sufficient such that the hyaluronan-degrading enzyme retains at least 50% of the initial hyaluronidase activity for at least three (3) days at 37°C.

126. The composition of claim 125, wherein the $MgCl_2$ concentration is between or about between 50 mM to 150 mM, 75 mM to 125 mM or 80 mM to 100 mM, inclusive.

127. The composition of claim 125 or claim 126, wherein the hyaluronan-degrading enzyme retains at least 50% of the initial hyaluronidase activity at 37°C for at least 4 days, 5 days, 6 days, one week, two weeks, three weeks, one month, two months, three months, four months, five months, six months or more.

128. The composition of any of claims 125-127, wherein the pH of the composition is between or about between 6.5 to 8.0, 6.5 to 7.4, 6.8 to 7.8, 7.0 to 7.6 or 6.8 to 7.2.

129. The composition of any of claims 125-128, wherein the composition further comprises a stabilizing agent.

130. The composition of any of claims 125-129, wherein the stabilizing agent is selected from among an amino acid, an amino acid derivative, an amine, a sugar, a polyol, a salt and a surfactant.

131. The composition of claim 130, wherein the stabilizing agent is a surfactant and the amount of surfactant, as a % of mass concentration (w/v) in the formulation, is between or about between 0.0005% to 1.0%, 0.0005% to 0.005%, 0.001% to 0.01%, 0.01% to 0.5%, 0.01% to 0.1%, 0.01% to 0.05%, or 0.01% to 0.02%, inclusive.

132. The composition of claim 130 or claim 131, wherein the surfactant is selected from among a polypropylene glycol, polyethylene glycol, glycerin, sorbitol, poloxamer and polysorbate.

133. The composition of any of claims 130-132, wherein the surfactant is selected from among poloxamer 188, polysorbate 20 and polysorbate 80.

134. The composition of any of claims 125-133, wherein the composition comprises an antioxidant.

135. The composition of claim 134, wherein the antioxidant is selected from among cysteine, tryptophan and methionine.

136. The composition of claim 135, wherein the antioxidant is methionine.

137. The composition of any of claims 134-136, wherein the antioxidant is at a concentration from between or from about between 5 mM to 50 mM, 5 mM to 40 mM, 5 mM to 20 mM or 10 mM to 20 mM, inclusive.

138. The composition of any of claims 125-137, comprising a sufficient amount of a buffering agent to maintain the pH range of between or about between 6.5 to 8.0, 6.8 to 7.8, 7.0 to 7.6, 6.5 to 7.2, or 6.8 to 7.4.

139. The composition of claim 138, wherein the buffering agent is selected from among Tris, histidine, phosphate and citrate.

140. The composition of claim 138 or claim 139, wherein the buffering agent is histidine hydrochloride.

141. The composition of any of claims 138-140, wherein the concentration of the buffering agent is between or is between about 1 mM to 100 mM, 10 mM to 80 mM, 5 mM to 50 mM or 20 mM to 40 mM.

142. The composition of any of claims 125-141, wherein the hyaluronan-degrading enzyme is a hyaluronidase or a chondroitinase.

143. The composition of any of claims 125-142, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is active at neutral pH.

144. The composition of any of claims 125-143, wherein the hyaluronan-degrading enzyme lacks a glycosylphosphatidylinositol (GPI) anchor or is not membrane-associated when expressed from a cell; or the hyaluronan-degrading enzyme is a hyaluronan-degrading enzyme that contains C-terminal truncations of one or more amino acid residues to remove all or part of a GPI anchor.

145. The composition of any of claims 125-144, wherein the hyaluronan-degrading enzyme is a hyaluronidase that is a PH20 or a C-terminally truncated fragment thereof.

146. The composition of any of claims 125-145, wherein the hyaluronan-degrading enzyme is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273.

147. The composition of any of claims 125-146, wherein the hyaluronan-degrading enzyme is a C-terminal truncated PH20 that comprises a sequence of amino acids set forth in any of SEQ ID NOS: 4-9.

148. The composition of any of claims 125-147, wherein the amount of a hyaluronan-degrading enzyme is between or about between 10 U/mL to 20,000 U/mL, 50 U/mL to 15,000 U/mL, 50 U/mL to 10,000 U/mL, 50 U/mL to 5000 U/mL, 50 U/mL to 4000 U/mL, 100 U/mL to 10000 U/mL, 100 U/mL to 5000 U/mL, 100 U/mL to 2000 U/mL, 300 U/mL to 5000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 5000 U/mL, 600 U/mL to 2000 U/mL, 100 U/mL to 1000 U/mL, 200 U/mL to 800 U/mL, 100 U/mL to 500 U/mL, or 150 U/mL to 300 U/ml, inclusive.

149. The composition of any of claims 125-148, wherein:

the pH of the composition is between or about between 6.5 to 7.2; and

the composition comprises:

a hyaluronan-degrading enzyme in an amount that is between or about between 100 U/mL to 500 U/mL, inclusive;

$MgCl_2$ at a concentration that is between or about between 50 mM to 150 mM, inclusive;

a surfactant that is polysorbate 80 at a percentage (%) of mass concentration (w/v) of between or about between 0.01% to 0.05%, inclusive;

methionine at a concentration that is between or about between 5 mM to 20 mM, inclusive; and

histidine/HCl at a concentration that is between or about between 5 mM to 50 mM, inclusive.

150. The stable co-formulation or composition of any of claims 1-149, wherein the volume of the composition is between or about between 0.5 mL to 50 mL, 1 mL to 40 mL, 1 mL to 20 mL, 1 mL to 10 mL, or 3 mL to 10 mL, inclusive.

151. The stable co-formulation or composition of any of claims 1-150 that is formulated for delivery using a vial, syringe, pen, reservoir for a pump or a closed loop system.

152. The stable co-formulation or composition of any of claims 1-151 that is formulated for delivery using a continuous subcutaneous insulin infusion.

153. The stable co-formulation or composition of any of claims 1-152, wherein the pH is or is about between 6.8 to 7.2

154. A syringe or vial, comprising the stable co-formulation or composition of any of claims 1-153.

155. A closed loop system, comprising the stable co-formulation or composition of any of claims 1-153.

156. An insulin pump, comprising the stable co-formulation or composition of any of claims 1-153.

157. An insulin pen, comprising the stable co-formulation or composition of any of claims 1-153.

158. A method of treating diabetes, comprising administering to a subject a therapeutically effective amount of a stable co-formulation or composition of any of claims 1-153.

159. The method of claim 158, wherein the diabetes is selected from among type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes.

160. A method for controlling blood glucose levels in a subject, comprising administering to a subject a therapeutically effective amount of a stable co-formulation or composition of any of claims 1-153.

161. The method of any of claims 158-160, further comprising administering a different anti-diabetic drug.

162. A stable co-formulation or composition of any of claims 1-153 for use in treating diabetes or for use in controlling blood glucose levels in a subject.

163. Use of a stable co-formulation or composition of any of claims 1-153 for treating diabetes or for controlling blood glucose levels in a subject.

164. Use of stable co-formulation or composition of any of claims 1-153 for the manufacture of a medicament for treating diabetes or for controlling blood glucose levels in a subject.

165. The stable co-formulation or composition or use of any of claims 162-164, wherein the diabetes is selected from among type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes.

CLAIMS:

1. A composition, comprising:

a hyaluronidase; and

lysyl lysine (Lys-Lys) in an amount to render the hyaluronidase stable.

2. The composition of claim 1, wherein the Lys-Lys concentration is between 5 mM to 120 mM, 10 mM to 100 mM, 5 mM to 50 mM, 10 mM to 50 mM, 30 mM to 110 mM, 30 mM to 80 mM, 50 mM to 100 mM or 100 mM to 120 mM.

3. The composition of claim 1, wherein the Lys-Lys concentration is 5 mM to 300 mM.

4. The composition of claim 1 or claim 3, wherein the Lys-Lys concentration is 50 mM to 150 mM, inclusive.

5. The composition of any of claims 1-4, wherein the concentration of hyaluronidase is at least 10 U/mL.

6. The composition of any of claims 1-5, wherein the amount of hyaluronidase is between 10 U/mL to 5000 U/mL, inclusive.

7. The composition of any of claims 1-6, wherein the formulation further comprises a stabilizing agent selected from among an amino acid, an amino acid derivative, an amine, a sugar, a polyol, a salt and a surfactant.

8. The composition of claim 7, wherein the stabilizing agent is a surfactant and the amount of surfactant, as a % of mass concentration (w/v) in the formulation, is between 0.0005% to 1.0%, 0.0005% to 0.005%, 0.001% to 0.01%, 0.01% to 0.5%, 0.01% to 0.1%, 0.01% to 0.05%, or 0.01% to 0.02%, inclusive.

9. The composition of claim 7 or claim 8, wherein the surfactant is selected from among a polypropylene glycol, polyethylene glycol, glycerin, sorbitol, poloxamer and polysorbate.

10. The composition of claim 7 or claim 8, wherein the surfactant is selected from among poloxamer 188, polysorbate 20 and polysorbate 80.

11. The composition of any of claims 1-10, wherein the composition comprises an antioxidant or a tonicity modifier.

12. The composition of any of claims 1-11, comprising a sufficient amount of a buffering agent to maintain the pH range of between 6.5 to 8.0, 6.8 to 7.8, 7.0 to 7.6, 6.5 to 7.2, or 6.8 to 7.4, inclusive, wherein the buffering agent is selected from among Tris, histidine, phosphate and citrate.

13. The composition of any of claims 1-12, wherein the hyaluronidase is a soluble hyaluronidase that is active at neutral pH.

14. The composition of claim 13, wherein the soluble hyaluronidase is a PH20 or a C-terminally truncated fragment thereof.

15. The composition of claim 13 or claim 14, wherein the soluble PH20 polypeptide is selected from ovine PH20, bovine PH20 and a soluble human PH20,

wherein the soluble human PH20 lacks all or a portion of the glycosylphosphatidylinositol (GPI) anchor attachement sequence.

16. The composition of any of claims 1-15, wherein the hyaluronidase is a PH20 polypeptide that has the sequence of amino acids set forth in any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273, or a sequence of amino acids that exhibits at least 91%, or more sequence identity to any of SEQ ID NOS: 4-9, 47-48, 234-254, and 267-273.

17. The composition of any of claims 14-16, wherein the hyaluronidase is a C-terminal truncated PH20 that comprises the sequence of amino acids set forth in any of SEQ ID NOS: 4-9.

18. The composition of any of claims 1-4 and 7-17, wherein:

the amount of a hyaluronidase is between 10 U/mL to 20,000 U/mL, 50 U/mL to 15,000 U/mL, 50 U/mL to 10,000 U/mL, 50 U/mL to 5000 U/mL, 50 U/mL to 4000 U/mL, 100 U/mL to 10000 U/mL, 100 U/mL to 5000 U/mL, 100 U/mL to 2000 U/mL, 300 U/mL to 5000 U/mL, 300 U/mL to 2000 U/mL, 600 U/mL to 5000 U/mL, 600 U/mL to 2000 U/mL, 100 U/mL to 1000 U/mL, 200 U/mL to 800 U/mL, 100 U/mL to 500 U/mL, or 150 U/mL to 300 U/ml, inclusive; or

the amount of a hyaluronidase is at least or is 30 U/mL, 35 U/mL, 40 U/mL, 50 U/mL, 100 U/mL, 150 U/mL, 200 U/mL, 250 U/mL, 300 U/mL, 350 U/mL, 400 U/mL, 450 U/mL, 500 U/mL, 600 U/mL, 700 U/mL, 800 U/mL, 900 U/mL, 1000 U/mL, 2000 U/mL, 3000 U/mL, 4000 U/mL, 5000 U/mL, 10000 U/mL, 15000 U/mL or 20000 U/mL.

19. The composition of any of claims 1-18, wherein:

the pH of the composition is between 6.5 to 7.2;

and the composition comprises:

a hyaluronidase in an amount that is between 100 U/mL to 500 U/mL, inclusive;

Lys-Lys at a concentration that is between 5 mM to 30 mM, inclusive;

NaCl at a concentration less than 140 mM NaCl;

a surfactant that is polysorbate 80 at a percentage (%) of mass concentration (w/v) of between 0.01% to 0.05%, inclusive;

methionine at a concentration that is between 5 mM to 20 mM, inclusive; and

sodium phosphate at a concentration that is between 5 mM to 50 mM, inclusive.

20. The composition of any of claims 1-19, further comprising a fast-acting insulin.

21. The composition of claim 20, wherein the concentration of Lys-Lys is 30 mM to 120 mM, 50 mM to 105 mM or 80 mM to 100 mM, inclusive.

22. The composition of claim 20 or claim 21, wherein the fast-acting insulin is a regular insulin or a fast-acting insulin analog.

23. The composition of claim 22, wherein the fast-acting insulin is a regular insulin and the regular insulin is a human insulin or pig insulin.

24. The composition of claim 22, wherein the fast-acting insulin is an insulin analog and the insulin analog is selected from among insulin aspart, insulin lispro and insulin glulisine.

25. The composition of claim 24, wherein the insulin analog is selected from among an insulin having an A chain with a sequence of amino acids set forth in SEQ NOS:103 and a B chain having a sequence of amino acids set forth in any of SEQ NOS:147-149.

26. The composition of any of claims 20-25, wherein the amount of fast-acting insulin is between 10 U/mL to 1000 U/mL, 20 U/mL to 500 U/mL, 50 U/mL to 300 U/mL or 200 U/mL to 800 U/mL, inclusive.

27. The composition of any of claims 1-26 that is for single dosage administration or is for multiple dosage administration.

28. The composition of claim 27, wherein the composition is for multiple dosage administration and comprises an anti-microbially effective amount of a preservative or mixture of preservatives.

29. The composition of any of claims 1-28, wherein:

the pH of the composition is between 6.8 to 7.4; and

the composition comprises:

a hyaluronidase that is a PH20 in an amount between 100 U/mL to 1000 U/mL, inclusive;

a fast-acting insulin analog that is insulin glulisine is an amount between 10 U/mL to 1000 U/mL, inclusive;

Lys-Lys at a concentration between 50 mM to 105 mM, inclusive;

NaCl at a concentration of less than 100 mM;

a surfactant that is polysorbate 20 at a percentage (%) of mass concentration (w/v) of between 0.0005% to 0.005%, inclusive;

methionine at a concentration between 5 mM to 20 mM, inclusive; and

a preservative(s) that comprises phenol at a percentage (%) of mass concentration (w/v) of between 0.1% to 0.25% and m-cresol at a % w/v of between 0.05% to 0.2%.

30. The composition of any of claims 1-28, wherein:

the pH of the composition is between 6.8 to 7.4; and

the composition comprises:

a hyaluronidase that is a PH20 in an amount between 100 U/mL to 1000 U/mL, inclusive;

a fast-acting insulin analog that is insulin aspart or insulin lispro is an amount between 10 U/mL to 1000 U/mL, inclusive;

Lys-Lys at a concentration between 80 mM to 100 mM, inclusive;

NaCl at a concentration of less than 30 mM;

a surfactant that is polysorbate 20 at a percentage (%) of mass concentration (w/v) of between 0.0005% to 0.005%, inclusive;

methionine at a concentration between 5 mM to 20 mM, inclusive; and

a preservative(s) that comprises phenol at a percentage (%) of mass concentration (w/v) of between 0.1% to 0.25% and m-cresol at a % w/v of between 0.05% to 0.2%.

31. A syringe or vial, comprising the stable composition of any of claims 1-30.

32. A closed loop system, comprising the stable composition of any of claims 1-30.

33. An insulin pump, comprising the stable composition of any of claims 1-30.

34. An insulin pen, comprising the stable composition of any of claims 1-30.

35. Use of the composition of any of claims 20-30 for treating diabetes or for controlling blood glucose levels in a subject.

36. The use of claim 35, wherein the diabetes is selected from among type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes

37. Use of the composition of any of claims 20-30 for the manufacture of a medicament for treating diabetes or for controlling blood glucose levels in a subject.

38. The use of claim 37, wherein the diabetes is selected from among type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes