Abstract: What is described is a pharmaceutical formulation for intranasal administration of exendin to a mammal, wherein the formulation comprises a therapeutically effective amount of an exendin, a viscosity enhancer, methyl-β-cyclodextrin, a surfactant, tartrate buffer to control pH and a chelating agent for cations, and wherein such exendin dosage form exhibits at least 95% exenatide recovery after storage for at least 365 days at 5°C.
1. An aqueous pharmaceutical formulation for intranasal administration of exendin to a mammal, comprising an exendin, tartrate buffer, methyl-β-cyclodextrin, a viscosity enhancer selected from gelatin, methylcellulose or hydroxypropylmethylcellulose, and a surfactant selected from nonionic polyoxyethylene ether, fusidic acid and its derivatives, sodium taurodihydrofusidate, L-α-phosphatidylcholine didecanoyl, polysorbate 80, polysorbate 20, polyethylene glycol, cetyl alcohol, polyvinylpyrrolidone, polyvinyl alcohol, lanolin alcohol or sorbitan monooleate, wherein the viscosity enhancer is present in an amount sufficient to provide a formulation viscosity up to about 150 cps.

2. The formulation of claim 1, wherein the exendin is exenatide.

3. The formulation of claim 1, wherein the surfactant is L-α-phosphatidylcholine didecanoyl.

4. The formulation of claim 1, further comprising a chelator selected from ethylene diamine tetraacetic acid or ethylene glycol tetraacetic acid.

5. The formulation of claim 4, wherein the chelator is ethylenediamine tetraacetic acid.

6. The formulation of claim 1, further comprising at least one tonicifier.

7. The formulation of claim 6, wherein the tonicifier is a salt.

8. The formulation of claim 7, wherein the salt is sodium chloride.

9. The formulation of claim 6, wherein the tonicifier is a polyol.

10. The aqueous formulation of claim 9, wherein the polyol is selected from lactose, sorbitol, trehalose, sucrose, mannose, mannitol, maltose, or derivatives and homologs thereof.
11. The formulation of claim 1, further comprising a preservative selected from chlorobutanol, methyl paraben, propyl paraben, butyl paraben, benzalkonium chloride, benzethonium chloride, sodium benzoate, sorbic acid, phenol, or ortho-, meta- or para-cresol.

12. The formulation of claim 1, wherein the formulation has a pH of about 2 to about 8.

13. The formulation of claim 1, wherein the viscosity enhancer is gelatin.

14. The formulation of claim 1, wherein the viscosity enhancer is methylcellulose or hydroxypropylmethylcellulose.

15. The formulation of claim 1, wherein the viscosity is about 1.5 to about 10.0 cps.

16. The formulation of claim 1, wherein the viscosity is up to about 5 cps.

17. The formulation of claim 1, wherein the viscosity is up to about 10 cps.

18. The formulation of claim 1, wherein the viscosity is up to about 20 cps.

19. The formulation of claim 1, wherein the viscosity is up to about 30 cps.

20. The formulation of claim 1, wherein the viscosity is up to about 50 cps.

21. The formulation of claim 1, wherein the viscosity is about 3.7 to about 5.0 cps.

22. An exendin dosage form suitable for multi-use administration comprising a sealed bottle containing a therapeutically effective amount of an aqueous pharmaceutical formulation of any of claims 1-21 for treating hyperglycemia, diabetes mellitus, dyslipidemia, suppressing appetite, promoting weight loss, decreasing food intake, or treating obesity in a mammal.
23. The exendin dosage form of claim 22, having at least about 98% recovery of exendin after at least 30 days at 5°C storage.

24. The exendin dosage form of claim 22, having at least about 98% recovery of exendin after 60 days at 5°C storage.

25. The exendin dosage form of claim 22, having at least about 96% recovery of exendin after 90 days at 5°C storage.

26. The exendin dosage form of claim 22, having at least about 95% recovery of exendin after 365 days at 5°C storage.

27. The exendin dosage form of claim 22, having at least about 96% recovery of exendin after at least 30 days at 25°C storage.

28. The exendin dosage form of claim 22, having at least about 93% recovery of exendin after 60 days at 25°C storage.

29. The exendin dosage form of claim 22, having at least about 89% recovery of exendin after 90 days at 25°C storage.

30. An exendin dosage form suitable for multi-use administration comprising a bottle containing an aqueous pharmaceutical formulation and an actuator effective for intranasal administration of the formulation of any of claims 1-21, wherein the formulation comprises a therapeutically effective amount of exendin, and wherein such dosage form exhibits at least 89% exenatide recovery after storage for at least 90 days at 25°C.

31. The dosage form of claim 30, wherein the formulation has a pH of about 2 to about 8.

32. The dosage form of claim 30, wherein the concentration of exendin is at least about 20 µg/ml.
33. The dosage form of claim 30, wherein the concentration of exendin is at least about 100 µg/ml.

34. The dosage form of claim 30, wherein the concentration of exendin is at least about 200 µg/ml.

35. The dosage form of claim 30, wherein the concentration of exendin is at least about 1 mg/ml.

36. The dosage form of claim 30, wherein the concentration of exendin is at least about 2 mg/ml.

37. The dosage form of claim 30, wherein the concentration of exendin is at least about 6 mg/ml.

38. The dosage form of claim 30, wherein the concentration of exendin is at least about 12 mg/ml.

39. The dosage form of claim 30, wherein said dosage form is suitable for intra-nasal administration to achieve a dose of from about 2 µg to about 1800 µg of said exendin.

40. The dosage form of claim 30, wherein said dosage form is suitable for intra-nasal administration to achieve a dose of from about 100 µg to about 600 µg of said exendin.

41. The dosage form of claim 30, wherein the formulation comprises at least about 1 mg/mL of ethylene diamine tetraacetic acid.

42. The dosage form of claim 30, wherein the formulation comprises at least about 10 mg/mL of ethylene diamine tetraacetic acid.

43. The exendin dosage form of claim 30, wherein the formulation comprises at least about 50 mg/mL of ethylene diamine tetraacetic acid.
44. The dosage form of claim 30, further comprising a preservative selected from chlorobutanol or benzalkonium chloride.

45. An aqueous solution for intranasal pharmaceutical delivery of exendin, comprising an exendin, one or more viscosity enhancers that increase the viscosity of the formulation to greater than about 1.5 cps, methyl-β-cyclodextrin and a surfactant, wherein the aqueous solution consists of aerosolized, liquid droplets having an average volume-mean particle size (Dv, 50) greater than about 10 microns.

46. The aqueous solution of claim 45, where in the liquid droplets have an average volume-mean particle size (Dv, 50) between about 5 micron and 500 microns.

47. The aqueous solution of claim 45, where in the liquid droplet have an average volume-mean particle size (Dv, 50) between about 10 and 100 microns.

48. A method for treating a metabolic disease in a human or animal subject comprising administering transmucosally to the subject an aqueous pharmaceutical formulation of any of claims 1-21, wherein the amount of exendin administered to the subject is sufficient to decrease blood glucose levels in the subject.

49. The method of claim 48, wherein the formulation is administered to the subject intranasally.

50. The method of claim 48, wherein the exendin is exenatide.

51. The method of claim 48, wherein the metabolic disease is selected from insulin dependent diabetes mellitus (IDDM), gestational diabetes, non insulin-dependent diabetes mellitus (NIDDM), obesity or dyslipidemia.

52. The method of claim 48, wherein the formulation comprises about 0.001 pmol to about 100 pmol of the exendin per kg of body weight of the subject.

53. The method of claim 48, wherein the formulation comprises about 0.01 pmol to about 10 pmol of the exendin per kg of body weight of the subject.
54. The method of claim 48, wherein the formulation comprises about 0.1 pmol to about 5 pmol of the exendin per kg of body weight of the subject.

55. The method of claim 48, wherein the pharmaceutical formulation is administered to the subject prior to a meal.

56. The method of claim 48, wherein the subject is a human subject and such administration decreases glucose levels to about the levels obtained by a subcutaneous injection of five micrograms of exenatide.

57. The method of claim 48, wherein such administration decreases glucose levels to the about 30% below placebo levels.

58. The method of claim 48, wherein the formulation is administered to the subject between one time a week and eight times a day for a period of at least one week.

59. A method for treating a metabolic disease in a human or animal subject comprising administering transmucosally to the subject an aqueous pharmaceutical formulation of claims 1-21, wherein the formulation comprises about 20 µg to about 400 µg of the exendin.

60. The method of claim 59, wherein the formulation is administered to the subject intranasally.

61. The method of claim 59, wherein the metabolic disease is selected from insulin dependent diabetes mellitus (IDDM), gestational diabetes, non insulin-dependent diabetes mellitus (NIDDM), obesity or dyslipidemia.

62. The method of claim 59, wherein the formulation comprises about 0.001 pmol to about 100 pmol of the exendin per kg of body weight of the subject.

63. The method of claim 59, wherein the formulation comprises about 0.01 pmol to about 10 pmol of the exendin per kg of body weight of the subject.
64. The method of claim 59, wherein the formulation comprises about 0.1 pmol to about 5 pmol of the exendin per kg of body weight of the subject.

65. The method of claim 59, wherein the pharmaceutical formulation is administered to the subject prior to a meal.

66. The method of claim 59, wherein the subject is a human subject and such administration decreases glucose levels to about the levels obtained by a subcutaneous injection of five micrograms of exenatide.

67. The method of claim 59, wherein such administration decreases glucose levels to the about 30% below placebo levels.

68. A formulation of any of claims 1-21 as a pharmaceutical for transmucosal delivery to a human or animal subject.

69. Use of a formulation of any of claims 1-21, for the manufacture of a medicament for the transmucosal treatment of a metabolic disorder.

70. Use of claim 69, wherein the metabolic disease is selected from insulin dependent diabetes mellitus (IDDM), gestational diabetes, non insulin-dependent diabetes mellitus (NIDDM), obesity or dyslipidemia.