CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical spray formulation, comprising:

(a) from about 1% to about 25% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water, ethanol, propylene glycol, or a combination thereof; and

(b) one or more of an antioxidant, an antimicrobial preservative, an isotonicity agent, an absorption enhancer, a viscosity modifier, or a buffering agent;

wherein the formulation is configured to be administered into a nostril of a subject as a nasal spray that yields a plasma concentration of at least 0.4 ng/mL within 1 minute of administration.

2. The pharmaceutical spray formulation of claim 1, wherein the pH of the formulation is from about 4.0 to about 6.5.

3. The pharmaceutical spray formulation of claim 1 or claim 2, wherein the antioxidant comprises sodium bisulfite or sodium metabisulfite at a concentration from about 0.01% to about 0.1% (w/w).

4. The pharmaceutical spray formulation of any one of claims 1-3, wherein the antimicrobial preservative comprises chlorobutanol or chlorobutanol hemihydrate at a concentration from about 0.1% to about 1% (w/w).

5. The pharmaceutical spray formulation of any one of claims 1-4, wherein the isotonicity agent comprises sodium chloride at a concentration from about 0.1% to about 1% (w/w).

6. The pharmaceutical spray formulation of any one of claims 1-5, wherein the viscosity modifier comprises hypromellose at a concentration from about 0.01% to about 0.2% (w/w).

7. The pharmaceutical spray formulation of any one of claims 1-6, wherein the buffering agent comprises citric acid or citric acid monohydrate at a concentration from about 0.1% to about 1% (w/w).

8. The pharmaceutical spray formulation of any one of claims 1-6, comprising from about 1% to about 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

9. The pharmaceutical spray formulation of claim 1, wherein the pharmaceutical spray formulation comprises sodium metabisulfite, sodium chloride, hypromellose, citric acid monohydrate, diethylene glycol monoethyl ether, and chlorobutanol hemihydrate.

10. The pharmaceutical spray formulation of claim 9, comprising from about 1% to about 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, from about 0.01% to about 0.1% (w/w) of sodium metabisulfite, from about 0.1% to about 1% (w/w) sodium chloride, from about 0.01% to about 0.2% (w/w) hypromellose, from about 0.1% to about 1% (w/w) citric

acid monohydrate, from about 0.1% to about 5% (w/w) diethylene glycol monoethyl ether, and from about 0.1% to about 1% (w/w) chlorobutanol hemihydrate.

11. A stable pharmaceutical spray formulation, comprising:

(a) from about 1% to about 25% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water, ethanol, propylene glycol, or a combination thereof; and

(b) one or more of an antioxidant, an antimicrobial preservative, an isotonicity agent, an absorption enhancer, a viscosity modifier, or a buffering agent;

wherein the formulation is stable for a period of at least about one month at a temperature of at least about 20 °C.

12. The pharmaceutical spray formulation of claim 11, wherein the formulation is stable for a period of at least one month at a temperature of at least about 40 °C.

13. The pharmaceutical spray formulation of claim 11 or claim 12, wherein the formulation has no more than about 2% total impurities after storage for a period of at least about one month at a temperature of at least about 40 °C.

14. The pharmaceutical spray formulation of any one of claims 11-13, wherein the antioxidant comprises sodium bisulfite or sodium metabisulfite at a concentration from about 0.01% to about 0.1% (w/w).

15. The pharmaceutical spray formulation of any one of claims 11-14, wherein the antimicrobial preservative comprises chlorobutanol or chlorobutanol hemihydrate at a concentration from about 0.1% to about 1% (w/w).

16. The pharmaceutical spray formulation of any one of claims 11-15, wherein the isotonicity agent comprises sodium chloride at a concentration from about 0.1% to about 1% (w/w).

17. The pharmaceutical spray formulation of any one of claims 11-16, wherein the buffering agent comprises citric acid or citric acid monohydrate at a concentration from about 0.1% to about 1% (w/w).

18. A pharmaceutical spray formulation, comprising:

(a) from about 1% to about 25% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water, ethanol, propylene glycol, or a combination thereof; and

(b) one or more of an antioxidant, an antimicrobial preservative, an isotonicity agent, an absorption enhancer, a viscosity modifier, or a buffering agent;

wherein the absorption enhancer is diethylene glycol monoethyl ether.

19. The pharmaceutical spray formulation of claim 18, wherein the formulation comprises diethylene glycol monoethyl ether at a concentration from about 0.1% to about 5% (w/w).

20. The pharmaceutical spray formulation of claim 1, wherein the absorption enhancer comprises diethylene glycol monoethyl ether at a concentration of about 1% (w/w).

21. A pharmaceutical nasal spray formulation comprising:

(a) about 1% to about 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

(b) about 0.01% to about 0.1% (w/w) sodium bisulfite or sodium metabisulfite;

(c) about 0.005% to about 1% (w/w) of chlorobutanol or chlorobutanol hemihydrate; and

(d) one or more of diethylene glycol monoethyl ether, hypromellose, citric acid, citric acid monohydrate, sodium chloride, or any combination thereof; and

wherein the pharmaceutical nasal spray formation has a weight ratio of the epinephrine to the chlorobutanol or chlorobutanal hemihydrate of about 12:1 to about 30:1.

22. The pharmaceutical nasal spray formulation of claim 21, wherein the formulation comprises from about 0.2% to about 0.5% (w/w) of chlorobutanol or chlorobutanol hemihydrate.

23. The pharmaceutical nasal spray formulation of claim 21 or claim 22, wherein the formulation comprises no more than about 3% total impurities after storage for a period of one month at a temperature of about 40 °C.

24. The pharmaceutical nasal spray formulation of any one of claims 21-23, wherein the formulation comprises no more than about 2% total impurities after storage for a period of one month at a temperature of about 40 °C.

25. The pharmaceutical nasal spray formulation of claim 23 or claim 24, wherein the impurities comprise one or more selected from epinephrine sulfonic acid, adrenochrome, norepinephrine, and adrenalone.

26. The pharmaceutical nasal spray formulation of any one of claims 21-25, wherein the pharmaceutical nasal spray formulation comprises from about 2% to about 6.5% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water.

27. The pharmaceutical nasal spray formulation of any one of claims 21-26, wherein the pharmaceutical nasal spray formulation comprises hypromellose at a concentration from about 0.01% to about 0.2% (w/w).

28. The pharmaceutical nasal spray formulation of any one of claims 21-27, wherein the pharmaceutical nasal spray formulation comprises citric acid or citric acid monohydrate at a concentration from about 0.1% to about 1% (w/w).

29. The pharmaceutical nasal spray formulation of any one of claims 21-27, wherein the pharmaceutical nasal spray formulation comprises sodium chloride at a concentration of from about 0.1% to about 1% (w/w).

30. The pharmaceutical nasal spray formulation of any one of claims 21-25, wherein the pharmaceutical nasal spray formulation comprises diethylene glycol monoethyl ether, hypromellose, citric acid monohydrate, and sodium chloride.

31. The pharmaceutical nasal spray formulation of any one of claims 21-30, wherein the pharmaceutical nasal spray formulation comprises from about 0.1% to about 5% (w/w) of diethylene glycol monoethyl ether, from about 0.01% to about 0.2% (w/w) of hypromellose, from about 0.1% to about 1% (w/w) of citric acid monohydrate, and from about 0.1% to about 1% (w/w) sodium chloride.

32. The pharmaceutical nasal spray formulation of any one of claims 21-31, wherein the pharmaceutical nasal spray formulation comprises about 1% (w/w) of diethylene glycol monoethyl ether, about 0.1% (w/w) of hypromellose, about 0.4% (w/w) citric acid monohydrate, and about 0.4% (w/w)-sodium chloride.

33. The pharmaceutical nasal spray formulation of any one of claims 21-32, wherein the pH of the pharmaceutical nasal spray formulation is about 4.0 to about 6.5.

34. The pharmaceutical nasal spray formulation of any one of claims 21-33, wherein a spray of the pharmaceutical nasal spray formulation delivered into a nostril of a subject in need thereof is effective to treat at least one symptom of anaphylaxis, anaphylactic shock, a severe allergic reaction, or bronchial constriction.

35. The pharmaceutical nasal spray formulation of any one of claims 21-34, wherein a spray of the pharmaceutical nasal spray formulation yields a plasma concentration in a subject of at least 0.4 ng/mL within 1 minute of administration.

36. The pharmaceutical nasal spray formulation of claim 34 or claim 35, wherein each spray of the pharmaceutical nasal spray formulation is about 20 µL to about 250 µL.

37. The pharmaceutical nasal spray formulation of any one of claims 34-36, wherein each spray of the pharmaceutical nasal spray formulation delivers about 1 to about 10 mg of epinephrine.

38. A pharmaceutical nasal spray formulation comprising

(a) from about 1% to about 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

(b) from about 0.1% to about 5% (w/w) of diethylene glycol monoethyl ether;

(c) from about 0.01% to about 0.2% (w/w) of hypromellose;

(d) from about 0.01% to about 0.1% (w/w) of sodium metabisulfite;

(e) from about 0.1% to about 1.0% (w/w) of chlorobutanol hemihydrate;

(f) from about 0.1% to about 1.0% (w/w) of citric acid monohydrate; and

(g) from about 0.1% to about 1.0% % (w/w) sodium chloride,

wherein the pharmaceutical nasal spray formulation is an aqueous solution suitable for administration as a spray into a nostril of a human subject; and

wherein the formulation comprises no more than 4% total impurities after storage for a period of one month at a temperature of about 40 °C.

39. A pharmaceutical nasal spray formulation, comprising:

(a) about 6.5% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

(b) about 1% (w/w) of diethylene glycol monoethyl ether;

(c) about 0.1% (w/w) of hypromellose;

(d) about 0.05% (w/w) of sodium metabisulfite;

(e) about 0.21% (w/w) of chlorobutanol hemihydrate;

(f) about 0.42% (w/w) of citric acid monohydrate; and

(g) about 0.4% (w/w) sodium chloride,

wherein the pharmaceutical nasal spray formulation is an aqueous solution suitable for administration as a spray into a nostril of a human subject;

wherein the formulation comprises no more than 2% total impurities after storage for a period of one month at a temperature of about 40 °C.

40. A pharmaceutical nasal spray formulation, comprising:

(a) about 6 % (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

(b) about 1% (w/w) of diethylene glycol monoethyl ether;

(c) about 0.1% (w/w) of hypromellose;

(d) about 0.05% (w/w) of sodium metabisulfite;

(e) about 0.21% (w/w) of chlorobutanol;

(f) about 0.42% (w/w) of citric acid monohydrate; and

(g) about 0.4% (w/w) sodium chloride,

wherein the pharmaceutical nasal spray formulation is an aqueous solution suitable for administration as a spray into a nostril of a human subject; and

wherein the formulation comprises no more than 2% total impurities after storage for a period of one month at a temperature of about 40 °C.

41. The pharmaceutical nasal spray formulation of any one of claims 38-40, wherein the pH of the formulation is from about 4.0 to about 6.5.

42. The pharmaceutical nasal spray formulation of any one of claims 38-41, wherein a dose of the formulation is from about 100 µl to about 200 µl.

43. The pharmaceutical nasal spray formulation of any one of claims 38-42, wherein a dose of the formulation is about 100 µl.

44. A bi-dose nasal delivery device adapted for delivery of a pharmaceutical composition into a nostril of a human subject, comprising:

(a) the pharmaceutical composition configured as an aqueous pharmaceutical nasal spray formulation comprising

(i) from about 1% to about 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

(ii) from about 0.1% to about 5% (w/w) of diethylene glycol monoethyl ether;

(iii) from about 0.01% to about 0.2% (w/w) of hypromellose;

(iv) from about 0.01% to about 0.1% (w/w) of sodium bisulfite or sodium metabisulfite;

(v) from about 0.1% to about 1.0% (w/w) of chlorobutanol or chlorobutanol hemihydrate;

(vi) from about 0.1% to about 1% (w/w) of citric acid or citric acid monohydrate; and

(vii) from about 0.1% to about 1.0% (w/w) of sodium chloride; and

(b) a reservoir containing from about 125 μL to about 250 μL of the pharmaceutical composition,

wherein the bi-dose device is configured to administer the pharmaceutical composition into the nostril of the human subject as one or two nasal sprays.

45. The device of claim 44, wherein the device is a pre-primed device that is configured to be actuatable with one hand.

46. The device of claim 44 or claim 45, wherein the device is configured to deliver from about 100 μL to about 250 μL of the pharmaceutical composition from the reservoir upon each actuation of the device.

47. The device of any one of claims 44-46, wherein the pharmaceutical composition has a pH from about 4.0 to about 6.5.

48. The device of any one of claims 44-47, wherein one or more sprays take ~~the~~ **a** shape of a round plume with an ovality ratio less than about 2.0.

49. The device of any one of claims 44-48, wherein the pharmaceutical composition comprises about 2% or about 5% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

50. The device of any one of claims 44-49, wherein the pharmaceutical composition is stable for a period of at least about three months at a temperature of at least about 20 °C.

51. The device of any one of claims 44-50, wherein the pharmaceutical composition is stable for a period of at least one month at a temperature of at least about 40 °C.

52. The device of any one of claims 44-51, wherein the pharmaceutical composition comprises no more than 2% total impurities after storage for a period of at least one month at a temperature of at least about 40 °C.

53. A pre-primed device adapted for delivery of an aqueous pharmaceutical composition into one or both nostrils of a human subject, comprising a reservoir containing from about 125 μL to about 250 μL of the pharmaceutical composition, wherein the pharmaceutical composition comprises:

(a) from about 1% to about 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

(b) about 1% (w/w) of diethylene glycol monoethyl ether;

(c) from about 0.01% to about 0.2% (w/w) of hypromellose;

(d) from about 0.01% to about 0.1% (w/w) of sodium bisulfite or sodium metabisulfite;

(e) from about 0.1% to about 1.0% (w/w) of chlorobutanol or chlorobutanol hemihydrate;

(f) from about 0.1% to about 1% (w/w) of citric acid or citric acid monohydrate; and

(g) from about 0.1% to about 1.0% (w/w) of sodium chloride,

wherein the pre-primed device is configured to administer the pharmaceutical composition as one or more sprays into one or both nostrils of the human subject.