CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical nasal spray formulation comprising

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

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

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

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

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

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

(g) from 0.1% to 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 40 °C.

2. A pharmaceutical nasal spray formulation, comprising:

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

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

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

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

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

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

(g) 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 40 °C.

3. A pharmaceutical nasal spray formulation, comprising:

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

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

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

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

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

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

(g) 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 40 °C.

4. The pharmaceutical nasal spray formulation of any one of claims 1-3, wherein the pH of the formulation is from 4.0 to 6.5.

5. The pharmaceutical nasal spray formulation of any one of claims 1-4, wherein a dose of the formulation is from 20 µl to 250 µl.

6. The pharmaceutical nasal spray formulation of any one of claims 1-5, wherein a dose of the formulation is 100 µl.

7. 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 1% to 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

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

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

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

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

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

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

(b) a reservoir containing from 125 µL to 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.

8. The device of claim 7, wherein the device is a pre-primed device that is configured to be actuatable with one hand.

9. The device of claim 7 or claim 8, wherein the device is configured to deliver from 100 μL to 250 μL of the pharmaceutical composition from the reservoir upon each actuation of the device.

10. The device of any one of claims 7-9, wherein the pharmaceutical composition has a pH from 4.0 to 6.5.

11. The device of any one of claims 7-10, wherein one or more sprays take a shape of a round plume with an ovality ratio less than 2.0.

12. The device of any one of claims 7-11, wherein the pharmaceutical composition comprises 2%, 5%, 6%, or 6.5% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

13. The device of any one of claims 7-12, wherein the pharmaceutical composition is stable for a period of at least three months at a temperature of at least 20 °C.

14. The device of any one of claims 7-13, wherein the pharmaceutical composition is stable for a period of at least one month at a temperature of at least 40 °C.

15. The device of any one of claims 7-14, 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 40 °C.

16. 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 125 μL to 250 μL of the pharmaceutical composition, wherein the pharmaceutical composition comprises:

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

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

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

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

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

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

(g) from 0.1% to 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.

17. The pharmaceutical nasal spray formulation of claim 1, comprising from 4% to 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water.

18. The pharmaceutical nasal spray formulation of claim 1 or claim 17, comprising:

(a) from 4% to 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

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

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

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

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

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

(g) 0.4% (w/w) sodium chloride.

19. The pharmaceutical nasal spray formulation of claim 1 or claim 17, comprising 6.5% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water.

20. The pharmaceutical nasal spray formulation of claim 1 or claim 17, comprising 6% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water.

21. The pharmaceutical nasal spray formulation of any one of claims 1 or 17-20, wherein the pH of the formulation is from 4.0 to 6.5.

22. The pharmaceutical nasal spray formulation of any one of claims 1 or 17-21, wherein the formulation comprises no more than 2% total impurities after storage for a period of one month at a temperature of 40 °C.

23. The device of claim 7, wherein the pharmaceutical composition comprises from 4% to 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water.

24. The device of any one of claims 7-15 or 23, wherein the pharmaceutical composition comprises 6% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

25. The device of any one of claims 7-15 or 23, wherein the pharmaceutical composition comprises 6.5% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

26. The device of any one of claims 7-15 or 23, wherein the pharmaceutical composition comprises

(a) from 4% to 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

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

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

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

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

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

(g) 0.4% (w/w) sodium chloride.

27. The device of any one of claims 7-15 or 23, wherein the pharmaceutical composition comprises

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

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

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

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

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

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

(g) 0.4% (w/w) sodium chloride.

28. The device of any one of claims 7-15 or 23, wherein the pharmaceutical composition comprises

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

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

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

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

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

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

(g) 0.4% (w/w) sodium chloride.

29. The device of any one of claims 7-15, wherein the pharmaceutical composition comprises 2% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

30. The device of any one of claims 7-15 or 23-29, wherein one or more sprays take a shape of a round plume with a particle size distribution having a span of no more than 2.2 when measured at a distance of from 1 to 10 cm from the device.

31. The device of any one of claims 7-15 or 23-30, wherein one or more sprays take a shape of a round plume with a Dmax of less than 28 mm when measured at a distance of from 1 to 10 cm from the device.

32. The device of any one of claims 7-15 or 23-31, wherein the bi-dose device is configured to administer the pharmaceutical composition as a single spray in each nostril of the human subject.

33. The pre-primed device of claim 16, wherein the pharmaceutical composition comprises from 4% to 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water.

34. The pre-primed device of claim 16 or claim 33, wherein the pharmaceutical composition comprises 6% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

35. The pre-primed device of claim 16 or claim 33, wherein the pharmaceutical composition comprises 6.5% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

36. The pre-primed device of claim 16 or claim 33, wherein the pharmaceutical composition comprises

(a) from 4% to 10% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof, in water;

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

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

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

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

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

(g) 0.4% (w/w) sodium chloride.

37. The pre-primed device of claim 16 or claim 31, wherein the pharmaceutical composition comprises

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

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

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

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

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

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

(g) 0.4% (w/w) sodium chloride.

38. The pre-primed device of claim 16 or claim 31, wherein the pharmaceutical composition comprises

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

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

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

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

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

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

(g) 0.4% (w/w) sodium chloride.

39. The pre-primed device of claim 16, wherein the pharmaceutical composition comprises 2% (w/w) of epinephrine, or a pharmaceutically acceptable salt thereof.

40. The pre-primed device of claim 16, wherein the pre-primed device is configured to administer the pharmaceutical composition as a single spray in each nostril of the human subject.