treatment of anaphylaxis and other conditions comprising administering an intranasal formulation of epinephrine using a small compact unit dose sprayer device.

[0012] In one aspect, described herein is a nasal spray pharmaceutical formulation comprising between about 0.40 mg and about 2.4 mg of epinephrine, or a salt thereof. In another aspect, described herein is a nasal spray pharmaceutical formulation comprising between about 0.40 mg and about 2.4 mg of epinephrine, or a salt thereof, in a single dose of the nasal spray pharmaceutical formulation. In another aspect, described herein is a nasal spray pharmaceutical formulation comprising between about 0.40 mg and about 2.4 mg of epinephrine, or a salt thereof, in a single dose nasal spray pharmaceutical formulation. In some embodiments, the nasal spray pharmaceutical formulation comprises between about 0.40 mg and about 2.0 mg of epinephrine, or a salt thereof. In some embodiments, the nasal spray pharmaceutical formulation comprises between about 0.40 mg and about 1.8 mg of epinephrine, or a salt thereof. In some embodiments, a single dose of the nasal spray pharmaceutical formulation comprises between about 0.5 mg and about 2.0 mg of epinephrine, or a salt thereof. In some embodiments, a single dose of the nasal spray pharmaceutical formulation comprises between about 0.5 mg and about 1.5 mg of epinephrine, or a salt thereof. In some embodiments, a single dose of the nasal spray pharmaceutical formulation comprises between about about 0.5 mg and about 0.7 mg of epinephrine, or a salt thereof. In some embodiments, a single dose of the nasal spray pharmaceutical formulation comprises about 1.0 mg of epinephrine, or a salt thereof. In some embodiments, a single dose of the nasal spray pharmaceutical formulation comprises between about 1.3 mg and about 1.5 mg of epinephrine, or a salt thereof. In some embodiments, intranasal administration of a single dose of the nasal spray pharmaceutical formulation to a subject provides a plasma epinephrine concentration that are efficacious for the treatment of an acute hypersensitivity reaction. In some embodiments, the nasal spray pharmaceutical formulation is an aqueous solution, aqueous suspension, aqueous emulsion, non-aqueous solution, non-aqueous suspensions, non-aqueous emulsion, or dry powder.

[0012a] In one aspect, described herein is a nasal spray pharmaceutical formulation comprising between 0.40 mg and 2.4 mg of epinephrine, or a salt thereof, in a single dose of the nasal spray pharmaceutical formulation; wherein the nasal spray pharmaceutical formulation further comprises an absorption enhancer, wherein the absorption enhancer is an alkylglycoside; wherein the nasal spray pharmaceutical formulation is an aqueous solution; wherein the nasal spray pharmaceutical formulation has a pH between 2.0 and 6.0; and wherein the epinephrine, or the salt thereof, is the only pharmaceutically active compound in the

pharmaceutical formulation.

[0013] In one aspect, described herein is a nasal spray formulation comprising between about 0.40 mg and about 2.4 mg per dose of epinephrine, or a salt thereof, dispensed from the device. In some embodiments, described herein is a nasal spray formulation comprising between about 0.5 mg and about 2.0 mg of epinephrine, or a salt thereof, per dose dispensed from the device; between about 0.5 mg and about 1.5 mg of epinephrine, or a salt thereof, per dose dispensed from the device; between about 0.5 mg and about 0.7 mg of epinephrine, or a salt thereof, per dose dispensed from the device; about 1.0 mg of epinephrine, or a salt thereof, per dose dispensed from the device; or between about 1.3 mg and about 1.5 mg of epinephrine,

benzalkonium chloride; wherein the benzalkonium chloride is the sole absorption enhancement agent in the formulation or is in present in the formulation with one or more absorption enhancement agents. In some embodiments of the methods of treatment, the isotonicity agent is sodium chloride. In some embodiments of the methods of treatment, the stabilizing agent is EDTA. In some embodiments of the methods of treatment, the stabilizing agent is EDTA in an amount from about 0.001% (w/v) to about 1% (w/v). In some embodiments of the methods of treatment, the preservative is benzalkonium chloride. In some embodiments of the methods of treatment, the preservative is benzalkonium chloride in an amount from about 0.001% (w/v) to about 1% (w/v).

[0069a] In one aspect, described herein is a use of the formulation as described herein in the manufacture of a medicament for the treatment of a type-1 hypersensitivity reaction (systemic allergic reaction).

[0069b] In one aspect, described herein is a use of the nasal spray pharmaceutical formulation as described herein in the manufacture of a medicament for the treatment of anaphylaxis, wherein the medicament is to be intranasally administered.

[0069c] In one aspect, described herein is the nasal spray pharmaceutical formulation as described herein for use in therapy.

[0070] Articles of manufacture, which include packaging material, a nasal spray formulation described herein within the packaging material, and a label that indicates that the nasal spray formulation is used for the treatment of any of the conditions described herein (e.g. anaphylaxis) are provided.

[0071] Other objects, features and advantages of the compositions and methods described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF FIGURES

[0072] **Figure 1** shows the area under the plasma concentration versus time curve at time 0-120 minutes ($AUC_{0\text{-}120\ min}$) of epinephrine absorption at different dosages and routes of administration as disclosed in Srisawat *et al*., "A preliminary study of intranasal epinephrine administration as a potential route for anaphylaxis treatment," *Asian Pac J Allergy Immunol*,

2016 Mar;34(1):38-43, discussed below.

[0073] **Figure 2** shows the plasma epinephrine concentration versus time plots after administrations of IN saline, IN epinephrine at 5 mg, and IM epinephrine at 0.3 mg, as disclosed in Srisawat *et al*.

[0074] **Figure 3** shows the mean plasma epinephrine concentrations above baseline (pg/mL) *vs.* time (min) curves from the first clinical study described in Example 2A comparing 0.3 mg epinephrine IM and IN; the curve with squared represents IM, and the curve with circles, IN.

[0075] **Figure 4** shows the mean plasma epinephrine concentrations above baseline (pg/mL) *vs.* time (min) curves from the second clinical study described in Example 2B comparing 0.5,

CLAIMS

What is claimed is:

1. A nasal spray pharmaceutical formulation comprising between 0.40 mg and 2.4 mg of epinephrine, or a salt thereof, in a single dose of the nasal spray pharmaceutical formulation;

wherein the nasal spray pharmaceutical formulation further comprises an absorption enhancer, wherein the absorption enhancer is an alkylglycoside;

wherein the nasal spray pharmaceutical formulation is an aqueous solution;

wherein the nasal spray pharmaceutical formulation has a pH between 2.0 and 6.0; and

wherein the epinephrine, or the salt thereof, is the only pharmaceutically active compound in the pharmaceutical formulation.

2. The formulation of claim 1, wherein a single dose of the nasal spray pharmaceutical formulation comprises:

between 0.5 mg and 2.0 mg of epinephrine, or a salt thereof;
between 0.5 mg and 1.5 mg of epinephrine, or a salt thereof;
between 0.5 mg and 0.7 mg of epinephrine, or a salt thereof;
1.0 mg of epinephrine, or a salt thereof; or
between 1.3 mg and 1.5 mg of epinephrine, or a salt thereof.

3. The formulation of claim 1 or 2, wherein:

the alkylglycoside is a sugar joined to a hydrophobic alkyl;
the sugar is maltose, glucose, or sucrose; and
the hydrophobic alkyl comprises 8 to 20 carbon atoms.

4. The formulation of claim 1 or 2, wherein the alkylglycoside is selected from the group consisting of undecyl maltoside, dodecyl maltoside, tridecyl maltoside, tetradecyl maltoside, sucrose mono-dodecanoate, sucrose mono-tridecanoate, and sucrose mono-tetradecanoate.

5. The formulation of claim 1 or 2, wherein the alkylglycoside is dodecyl maltoside.

6. The formulation of any one of claims 1-5, wherein the formulation comprises, per dose, between 25 and 250 µL of the aqueous solution.

7. The formulation of any one of claims 1-5, wherein the formulation comprises, per dose, 25 µL, 50 µL, 75 µL, 100 µL, 125 µL, 150 µL, 175 µL, 200 µL, or 250 µL of the aqueous solution.

8. The formulation of any one of claims 1-7, wherein the nasal spray pharmaceutical formulation comprises:

one or more agents selected from isotonicity agents; stabilizing agents; preservatives; taste-masking agents; viscosity modifiers; antioxidants; buffers and pH adjustment agents.

9. The formulation of any one of claims 1-8:

wherein the nasal spray pharmaceutical formulation comprises a stabilizing agent,

wherein the stabilizing agent is ethylenediaminetetraacetic acid (EDTA) or a salt thereof;

wherein the formulation comprises a preservative,

wherein the preservative is benzalkonium chloride; and

wherein the nasal spray pharmaceutical formulation comprises an isotonicity agent,

wherein the isotonicity agent is dextrose, glycerin, mannitol, potassium chloride, or sodium chloride.

10. The formulation of claim 9, wherein the isotonicity agent is sodium chloride.

11. Use of the formulation of any one of claims 1-10 in the manufacture of a medicament for the treatment of a type-1 hypersensitivity reaction (systemic allergic reaction).

12. The use according to claim 11, wherein the type 1 hypersensitivity reaction is chosen from allergic asthma, allergic conjunctivitis, allergic rhinitis, anaphylaxis, angioedema, urticaria, eosinophilia, drug allergy and food allergy, optionally wherein the drug allergy is an antibiotic allergy.

13. Use of the nasal spray pharmaceutical formulation of claim 1 in the manufacture of a medicament for the treatment of anaphylaxis, wherein the medicament is to be intranasally administered.

14. The use according to claim 13, wherein the nasal pharmaceutical formulation comprises:

between 0.5 mg and 1.5 mg of epinephrine, or a salt thereof; or
between 0.5 mg and 0.7 mg of epinephrine, or a salt thereof; or
1.0 mg of epinephrine, or a salt thereof; or
between 1.3 mg and 1.5 mg of epinephrine, or a salt thereof.

15. The use according to claim 13 or 14, wherein:

the alkylglycoside is a sugar joined to a hydrophobic alkyl;
the sugar is maltose, glucose, or sucrose; and
the hydrophobic alkyl comprises 8 to 20 carbon atoms.

16. The use according to claim 13 or 14, wherein the alkylglycoside is selected from the group consisting of undecyl maltoside, dodecyl maltoside, tridecyl maltoside, tetradecyl maltoside, sucrose mono-dodecanoate, sucrose mono-tridecanoate, and sucrose mono-tetradecanoate.

17. The use according to claim 13 or 14, wherein the alkylglycoside is dodecyl maltoside.

18. The use according to any one of claims 13-17, wherein the formulation comprises, per dose, between 25 and 250 µL of the aqueous solution.

19. The use according to any one of claims 13-17, wherein the formulation comprises, per dose, 25 µL, 50 µL, 75 µL, 100 µL, 125 µL, 150 µL, 175 µL, 200 µL, or 250 µL of the aqueous solution.

20. The use according to any one of claims 13-19, wherein the intranasal formulation comprises:

an isotonicity agent;
a stabilizing agent;
an optional antioxidant;
an optional buffering agent;
a preservative; and
optional pH adjustment agents.

21. The use according to any one of claims 13-20, wherein the intranasal formulation has a pH between 3.0 and 5.0.

22. The nasal spray pharmaceutical formulation of any one of claims 1 to 10 for use in therapy.