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SUMMARY

The present disclosure relates to a novel crystalline epinephrine salt, the epinephrine malonate salt, as well as pharmaceutical compositions comprising said epinephrine salt, methods for preparing said epinephrine salt, and methods for treating patients comprising administering said epinephrine salt to the patient. In a preferred example, the polymorphic crystalline epinephrine malonate has an x-ray powder diffraction pattern identified in FIG. 1.

In one aspect, the present disclosure refers to an epinephrine malonate salt in crystalline form. In another aspect, the present disclosure refers to a pharmaceutical composition comprising epinephrine malonate salt and a pharmaceutically acceptable carrier. In certain examples, a pharmaceutical composition is provided comprising the epinephrine malonate salt. The pharmaceutical composition can be suitable for oral, rectal, intragastrical, topical, intracranial, intranasal, and parenteral administration. In a preferred example, the pharmaceutical composition can be a sublingual or buccal tablet. The pharmaceutical formulation can comprise a pharmaceutically effective amount of epinephrine malonate salt and one or more pharmaceutically acceptable excipients, including, *e.g.,* a filler (*e.g.*, microcrystalline cellulose) and a disintegrant (*e.g.*, cross-linked polyvinyl polypyrrolidine or a low-substituted hydroxypropyl cellulose). In certain examples, the pharmaceutical composition can further include a lubricant (*e.g.*, magnesium stearate) and a glidant (*e.g.*, silicon dioxide). In certain examples the pharmaceutical composition can further include a diluent (*e.g.*, mannitol) and/or a pH adjusting agent (*e.g.*, citric acid). The pharmaceutical composition can comprise epinephrine malonate in an amount of 0.3 to 10 mg. The pharmaceutical composition can further comprise a filler in an amount of 20 to 30% by weight and a disintegrant

in an amount of 5 to 15% by weight. In certain examples, the pharmaceutical composition can disintegrate in less than or equal to 30 seconds.

In certain example, a method for preparing said epinephrine malonate salt is provided. The method can comprise adding malonic acid to a solution of epinephrine base in a solvent (*e.g.*, ethanol). The malonic acid can be added to the solution at a ratio of at least 0.001:1, at least 0.01:1, at least 1:1, at least 2:1, at least 3:1, at least 5:1, at least 10:1, at least 25:1, at least 50:1, at least 100:1, at least 500:1 relative to epinephrine. The malonic acid can be added to the solution at a ratio less than or equal to 100:1, less than or equal to 500:1, less than or equal to 100:1, less than or equal to 75:1, less than or equal to 5:1, less than or equal to 3:1, less than or equal to 2:1, less than or equal to 1:1. In certain examples, the malonic acid can be added to the solution at a ratio between 0.01:1 and 3:1. In a preferred example, the malonic acid can be added to the solution at a 1:1 equivalent relative to epinephrine. The method can comprise stirring the solution and precipitating the salt out of solution. The method can further comprise filtering and drying the precipitate.

In certain examples, a method for treating a patient is provided. The method comprises administering a pharmaceutically effective amount of epinephrine malonate to a patient in need of such treatment, including for example, a patient inflicted with anaphylaxis.

BRIEF DESCRIPTION OF THE FIGURES

The accompanying figures, which are incorporated herein and form part of the specification, illustrate various embodiments of the present disclosure and, together with the description, further serve to explain the principles of the disclosure and to enable a person skilled in the pertinent art to make and use the embodiments disclosed herein.

CLAIMS

We claim:

1. An epinephrine malonate salt in crystalline form.

2. The epinephrine malonate salt of claim 1, wherein the crystalline form has an x-ray powder diffraction spectrum (copper, K-alpha-1) having one or more peaks expressed as 2 theta at about 12.1843, 13.4653, 14.2595, 14.6991, 15.8664, 17.3570, 17.9004, 19.5883, 20.4659, 21.5801, 22.3908, 22.9301, 23.8776, 24.6585, 25.3418, 26.0105, 26.4829, 25.3418, 26.0105, 26.4829, 27.2385, 27.8939, 29.4741, 33.2425, 34.2629, 34.8439.

3. A pharmaceutical composition comprising epinephrine malonate salt and a pharmaceutically acceptable carrier.

4. The pharmaceutical composition of claim 3, wherein the pharmaceutical composition is suitable for oral, rectal, intragastrical, topical, intracranial, intranasal, and parenteral administration.

5. The pharmaceutical composition of claim 3, wherein the pharmaceutical composition is suitable for sublingual or buccal administration.

6. The pharmaceutical composition of claim 5, wherein the pharmaceutical composition comprises a filler and a disintegrant.

7. The pharmaceutical composition of claim 6, wherein the filler is microcrystalline cellulose and the disintegrant is cross-linked polyvinyl polypyrrolidone.

8. The pharmaceutical composition of claim 7, wherein the filler is present in an amount of 20 to 30% by weight and the disintegrant is present in an amount of 5 to 15% by weight.

9. The pharmaceutical composition of claim 8, further comprising a lubricant and a glidant.

10. The pharmaceutical composition of claim 9, wherein the lubricant is magnesium stearate and the glidant is silicon dioxide.

11. The pharmaceutical composition of claim 10, further comprising a diluent.

12. The pharmaceutical composition of claim 11, wherein the diluent is mannitol.

13. The pharmaceutical composition of claim 12, further comprising citric acid.

14. The pharmaceutical composition of claim 5, wherein the composition comprises an amount of 0.3 to 10 mg of epinephrine free base.

15. The pharmaceutical composition of claim 5, wherein the pharmaceutical composition disintegrates in less than or equal to 30 seconds.