(b) an actuator having one or more orifices with an effective diameter of from about 0.12 mm to about 0.33 mm. In a preferred embodiment, the MDI comprises:

(a) a canister containing a formulation comprising API (e.g., epinephrine or a pharmaceutically acceptable salt thereof); and

(b) an actuator having one or more orifices with an effective diameter of from about 0.12 mm to about 0.33 mm. Preferably, the MDI is a pressurized metered dose inhaler.

[0008a] In a first aspect of the present disclosure, there is provided a pressurized oral metered dose inhaler comprising: (a) a canister containing a formulation comprising an active pharmaceutical ingredient (API) selected from epinephrine and a pharmaceutically acceptable salt thereof; a liquified propellant; and a co-solvent; and (b) an actuator having one or more orifices with an effective diameter of from 0.16 mm to 0.29 mm, wherein the API is in suspension.

[0009] In some aspects, the effective diameter of the one or more orifices of the actuator is from about 0.14 mm to about 0.31 mm; from about 0.16 mm to about 0.29 mm; from about 0.18 mm to about 0.22 mm; from about 0.20 mm to about 0.25 mm; or from about 0.21 mm to about 0.23 mm. In other aspects, the effective diameter of the one or more orifices of the actuator is about 0.22 mm or is 0.22 mm. In one embodiment, the one or more orifices are circular in form; alternately, the one or more orifices may be peanut-, clover-, cross- or slot-shaped. In one embodiment, the actuator has a single orifice. In another embodiment, the actuator has a plurality of orifices, e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 orifices, which may have the same shape or a combination of different shapes, such as those specified above. In one embodiment, the actuator has a plurality of orifices (e.g., circular orifices) that are disposed linearly (e.g., aligned vertically when the MDI is used). In one embodiment, the actuator has an effective orifice diameter as aforesaid and a sump volume of 15-20 mm^3, preferably 17-19 mm^3, most preferably 18 mm^3 and/or a land length (i.e., channel length of the outlet orifice) of 0.55-0.75 mm, preferably 0.60-0.70 mm, most preferably 0.65. In specific embodiments, the actuator has the configuration of a Bespak BK632 or BK679 actuator (comprising a single orifice of diameter 0.33 mm, a sump volume of 18 mm^3 and a land length of 0.65 mm), preferably the configuration of a Bespak BK634 or BK665 actuator (comprising a single orifice of diameter 0.30 mm, a sump volume of 18 mm^3 and a land length of 0.65 mm), more preferably the configuration of a Bespak BK638 (comprising a single orifice of diameter 0.25 mm, a sump volume of 18 mm^3 and a land length of 0.65 mm), most preferably the configuration of a Bespak BK633 or BK671 actuator (comprising a single orifice of diameter 0.22 mm, a sump volume of 18 mm^3 and a land length of 0.65 mm). In some embodiments, the actuator has a mouthpiece that extends about 1.5 to 3.5 cm, preferably about 2.0 to 3.0 cm, more preferably about 2.5 cm from the portion of the orifice that is nearest to the user.

[0010] In other aspects, the API (e.g., epinephrine) formulation in the metered dose inhaler of the present disclosure comprises:

(a) a suspension of API (e.g., epinephrine or a pharmaceutically acceptable salt thereof);

(b) a liquefied propellant; and

(c) a co-solvent.

[0011] In some aspects, the co-solvent is present from about 0.1% to about 4%; from about 0.1% to about 3%; or from about 0.1% to about 2% w/w based on the total weight of the formulation. In a preferred embodiment, the co-solvent is present at about 1% w/w based on the total weight of the formulation. In other aspects, the co-solvent is ethanol, isopropanol, propylene glycol, ethylene glycol, propane, butane, isobutene, pentane, dimethyl ether, diethyl ether, or mixtures thereof. In a preferred embodiment, the co-solvent is ethanol (preferably dehydrated ethanol).

[0012] In some aspects, the liquefied propellant is present from about 95% to about 99.5%; from about 96% to about 99%; or from about 97% to about 99% w/w based on the total weight of the formulation. In other aspects, the liquefied propellant is 1,1,1,2-tetrafluoroethane (HFA-134A), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227), or a mixture thereof. In a preferred embodiment, the liquefied propellant is 1, 1,1,2 - tetrafluoroethane (FIFA-134a).

[0013] In some aspects, the suspension of API (e.g., epinephrine or a pharmaceutically acceptable salt thereof) is present from about 0.1% to about 0.5%; from about 0.1% to about 0.4%; or from about 0.1% to about 0.3% w/w based on the total weight of the formulation. In a preferred embodiment, the API (e.g., epinephrine or pharmaceutical salt thereof) in the suspension. In some embodiments the API is epinephrine free base. In a preferred embodiment, the epinephrine or a pharmaceutically acceptable salt thereof comprises epinephrine free base at a concentration of 0.19% w/w based on the total weight of the formulation.

[0014] In further aspects, the API (e.g., epinephrine) formulation of the present disclosure may additionally comprise a surfactant, such as a surfactant selected from mono- or poly-sorbitan oleates, oleic acid, and lecithin. In a preferred embodiment, the formulation comprises polysorbate 80. In further aspects, the API (e.g., epinephrine) formulation of the present disclosure may additionally comprise an antioxidant, such as an antioxidant selected from thymol, tocopherol, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, propyl gallate, citric acid, sodium metabisulfite and sodium sulfite. In a preferred embodiment, the formulation comprises thymol. Preferably, the formulation is free of metabisulfite; more preferably the formulation is free of sulfites.

[0015] In another embodiment, the present disclosure provides a method of administering API (e.g., epinephrine) to a patient in need thereof or a method of treating a patient in need of API (e.g., epinephrine) using the disclosed metered dose inhaler. In some aspects, the present disclosure provides a use of API (e.g., epinephrine) for treating a patient in need of API (e.g., epinephrine) using the disclosed metered dose inhaler.

[0015a] In a second aspect of the present disclosure, there is provided a use of a formulation in the manufacture of a medicament for treating an acute allergic reaction, said formulation comprising: an active pharmaceutical ingredient (API) selected from epinephrine and a pharmaceutically acceptable salt thereof; a liquified propellant; and a co-solvent; and wherein said formulation is to be administered to a patient by oral inhalation using the pressurized oral metered dose inhaler.

CLAIMS:

1. A pressurized oral metered dose inhaler comprising:

(a) a canister containing a formulation comprising

an active pharmaceutical ingredient (API) selected from epinephrine and a pharmaceutically acceptable salt thereof;

a liquified propellant; and

a co-solvent; and

(b) an actuator having one or more orifices with an effective diameter of from 0.16 mm to 0.29 mm,

wherein the API is in suspension.

2. The pressurized oral metered dose inhaler of claim 1, wherein the liquified propellant has a vapor pressure of 5.5 bar to 5.9 bar (absolute) at 20^{o}C.

3. The pressurized oral metered dose inhaler of claim 2, wherein the liquified propellant has a vapor pressure of 5.7 bar (absolute) at 20^{o}C.

4. The pressurized oral metered dose inhaler of claim 1, wherein the effective diameter of the one or more orifices is from 0.18 mm to 0.27 mm.

5. The pressurized oral metered dose inhaler of claim 4, wherein the effective diameter of the one or more orifices is from 0.20 mm to 0.25 mm.

6. The pressurized oral metered dose inhaler of claim 5, wherein the effective diameter of the one or more orifices is from 0.21 mm to 0.23 mm.

7. The pressurized oral metered dose inhaler of claim 6, wherein the effective diameter of the one or more orifices is 0.22 mm.

8. The pressurized oral metered dose inhaler of any one of claims 1-7, wherein the one or more orifices are circular.

9. The pressurized oral metered dose inhaler of any one of claims 1-7, wherein the one or more orifices comprise one or more peanut-, clover-, cross- or slot-shaped orifices.

10. The pressurized oral metered dose inhaler of any one of claims 1-9, wherein the actuator has a single orifice.

11. The pressurized oral metered dose inhaler of any one of claims 1-10, wherein the co-solvent is present from 0.1% to 4% w/w based on the total weight of the formulation.

12. The pressurized oral metered dose inhaler of claim 11, wherein the co-solvent is present from 0.1% to 2% w/w based on the total weight of the formulation.

13. The pressurized oral metered dose inhaler of any one of claims 1-12, wherein the co-solvent is ethanol, isopropanol, propylene glycol, ethylene glycol, propane, butane, isobutene, pentane, dimethyl ether, diethyl ether, or a mixture thereof.

14. The pressurized oral metered dose inhaler of claim 13, wherein the co-solvent is ethanol.

15. The pressurized oral metered dose inhaler of any one of claims 1-14, wherein the liquefied propellant is present from 95% to 99.5% w/w based on the total weight of the formulation.

16. The pressurized oral metered dose inhaler of claim 15, wherein the liquefied propellant is present from 97% to 99% w/w based on the total weight of the formulation.

17. The pressurized oral metered dose inhaler of any one of claims 1-16, wherein the liquefied propellant is 1,1,1,2-tetrafluoroethane (HFA-134A), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227), or a mixture thereof.

18. The pressurized oral metered dose inhaler of any one of claims 1-17, wherein the API is present from 0.1% to 0.5% w/w based on the total weight of the formulation.

19. The pressurized oral metered dose inhaler of claim 18, wherein the API is present from 0.1% to 0.4% w/w based on the total weight of the formulation.

20. The pressurized oral metered dose inhaler of claim 19, wherein the API is present from 0.1% to 0.3% w/w based on the total weight of the formulation.

21. The pressurized oral metered dose inhaler of any one of claims 1-20, wherein the API is epinephrine free base.

22. The pressurized oral metered dose inhaler of any one of claims 1-21, wherein the API is selected from the hydrochloric, hydrobromic, phosphoric, sulfuric, perchloric, acetic, oxalic, maleic, tartaric, citric, succinic and malonic acid salts of epinephrine and the adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate and valerate salts of epinephrine.

23. The pressurized oral metered dose inhaler of any one of claims 1-22, wherein the formulation further comprises a surfactant.

24. The pressurized oral metered dose inhaler of any one of claims 1-23, wherein the formulation further comprises an antioxidant

25. The pressurized oral metered dose inhaler of any one of claims 1-10,
wherein:

the API is epinephrine free base in suspension at a concentration of 1.9% w/w based on the total weight of the formulation;

the liquefied propellant is 1,1,1,2-tetrafluoroethane (HFA-134a);

the co-solvent is ethanol at about 1% w/w based on the total weight of the formulation;

wherein the formulation further comprises

polysorbate 80; and

thymol,

and wherein the formulation is free of sulfites.

26. The pressurized oral metered dose inhaler of any one of claims 1-25, which is capable of delivering a dose of epinephrine or pharmaceutically acceptable salt thereof such that the

proportion of the delivered dose that reaches the larynx, pharynx, and lungs when the metered dose inhaler is in a transverse orientation is at least 90% of the proportion of the delivered dose that reaches the larynx, pharynx, and lungs when the metered dose inhaler is in an coaxial orientation, as determined with the Sectioned Alberta Idealized Throat at a flowrate of 30 L/min.

27. The pressurized oral metered dose inhaler of any one of claims 1-26, which is a limited-dose metered dose inhaler adapted for emergency use and provides up to 50 inhalation doses.

28. The pressurized oral metered dose inhaler of claim 27, which provides up to 20 inhalation doses.

29. The pressurized oral metered dose inhaler of claim 28, which provides up to 10 inhalation doses.

30. Use of a formulation in the manufacture of a medicament for treating an acute allergic reaction, said formulation comprising:

an active pharmaceutical ingredient (API) selected from epinephrine and a pharmaceutically acceptable salt thereof;

a liquefied propellant; and

a co-solvent;

and wherein said formulation is to be administered to a patient by oral inhalation using the pressurized oral metered dose inhaler as defined in any one of claims 1-29.

31. The use according to claim 30 wherein the acute allergic reaction is anaphylaxis.

32. The use according to claim 31, wherein two puffs of epinephrine are to be administered periodically until the patient shows a physiological response to the treatment.

33. The use according to claim 32 wherein the physiological response is:

(a) tachycardia, tremor or both; or

(b) the patient’s subjective awareness of body or hand tremor or patient’s subjective awareness of increased heart rate.

34. The use according to claim 31, wherein a therapeutically effective amount of epinephrine is to be administered using two puffs of the pressurized metered dose inhaler once every 2 minutes until the anaphylactic reaction ameliorates.

35. The use according to claim 31, wherein two puffs of epinephrine are to be administered every 60 seconds until clinical resolution of allergic symptoms is obtained.

36. The use according to claim 30 or 31, wherein the administration is by oral inhalation of 250 µg epinephrine (for example two puffs) periodically until the patient experiences subjective awareness of a physiological response to treatment.

37. The use according to claim 36, wherein the administration is by oral inhalation of 250 µg epinephrine (for example two puffs) every 30-90 seconds until the patient experiences subjective awareness of a physiological response to treatment.

38. The use according to claim 36, wherein the administration is by oral inhalation of 250 µg epinephrine (for example two puffs) about every 60 seconds until the patient experiences subjective awareness of a physiological response to treatment.

39. The use according to any one of claims 36-38, wherein the awareness of a physiological response is awareness of increased heart rate, awareness of body or hand tremor, or awareness of both increased heart rate and body or hand tremor.