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(54) Title: INHALABLE EPINEPHRINE FORMULATION

(57) Abstract: An inhalable epinephrine formulation is provided for which comprises a pharmaceutically acceptable salt of epinephrine or a pharmaceutically acceptable salt of an epinephrine derivative and a solid carrier without the need for further excipients. The formulation has demonstrated a surprising level of stability on storage.

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Inhalable Epinephrine Formulation

Technical Field

[1] This disclosure relates to an inhalable formulation comprising a pharmaceutically acceptable salt of epinephrine, or of an epinephrine derivative, and a dry powder inhaler containing the inhalable formulation.

Background

[2] Anaphylaxis is a severe, potentially life-threatening allergic reaction. It can be caused by a number of triggers including: certain foods, such as nuts, shellfish or eggs; insect venom, such as bee or wasp stings; certain medications, such as antibiotics or aspirin; general anaesthetics and latex. As a first response to the trigger, the immune system releases a flood of chemicals that can cause the body to go into shock. Common signs and symptoms of anaphylaxis include a rapid, weak pulse; swelling of the lips, tongue or throat; shortness of breath and difficulty breathing; skin rashes and itching; and stomach pain, nausea and vomiting. If the condition is not treated immediately, it can be fatal.

[3] The primary treatment of anaphylaxis is the administration of epinephrine. Epinephrine, also known as adrenaline, is a hormone and neurotransmitter that stimulates the sympathetic nervous system. There are several treatment methods for anaphylaxis using epinephrine which are currently known. Arguably the most well-known product is the EpiPen, an auto-injector for the self-administration of epinephrine. The subject is required to jab (inject) him- or herself with the needle (preferably in the thigh), resulting in the release of a set dose of epinephrine into the muscle tissue.

[4] While the technology certainly has benefits, one major downside of this product is the harshness of the treatment method. Many patients and caregivers are reluctant to inject themselves with a needle, consequently wasting essential time in the context of an emergent life-threatening reaction. Further, the hesitancy to administer epinephrine via intramuscular injection gives rise to less than optimal decision making – such as ‘wait and see’, or treat first with an oral anti-histamine approaches. The use of an auto-injector device also carries the risk of accidental needle injury.

[5] Dry powder inhalers (DPIs) in combination with inhalable dry powders are used in the treatment of diseases such as respiratory diseases, cardiovascular diseases, diabetes, obesity, and cancer, or symptoms associated with these and other diseases, for example, nausea, vomiting, pain, and inflammation by delivering a consistent dose of a pharmacological agent to the patients' airways through inhalation.

[6] U.S. patent publication no. 2018/0056022 to Liu et al discloses a positive pressure hand-actuated DPI and the use of the DPI in combination with a wide range of traditional Chinese medicines (TCM) to treat diseases and disorders. While it contemplates the delivery of pharmaceutical actives including epinephrine, it does not actually make or test any such pharmaceutical grade DPI formulations and so provides no guidance to the person of skill in the art as to their stability, flow properties or overall feasibility.

[7] DPIs present challenges in terms of suitable formulations that have the appropriate particle sizes containing the active ingredient and which maintain this throughout a reasonable storage time. It is essential to achieve the necessary balance between the components of the formulation so that the active ingredient can be delivered to the deep lungs to provide for a suitably rapid response time.

Summary

[8] In a first aspect, the disclosure resides in an inhalable formulation comprising:

(i) a pharmaceutically acceptable salt of epinephrine, or a derivative thereof; and

(ii) a solid carrier.

[9] In embodiments, the pharmaceutically acceptable salt of epinephrine, or derivative thereof, is present at between about 0.01 to about 15.0 mg per unit dose of the formulation.

[10] In embodiments, the epinephrine salt or epinephrine derivative salt is selected from the group consisting of the bitartrate, hydrochloride, maleate, malate, malonate, fumarate, and borate salts, and mixtures thereof.

[11] In embodiments, the epinephrine derivative is selected from the group consisting of norepinephrine, dopamine, 3-methoxytyramine, synephrine, *p*-octopamine and salts and mixtures thereof.

[12] In embodiments, the solid carrier is selected from the group consisting of sugars and sugar alcohols, including saccharides and polysaccharides, such as lactose, mannose, sucrose, mannitol, trehalose, citrates, amino acids such as glycine, L-leucine, isoleucine, trileucine, tartrates, methionine, vitamin A, zinc citrate, trisodium citrate, zinc chloride, polyvinylpyrrolidone, phospholipids including diphosphotidylcholine and the like.

[13] In an embodiment, the solid carrier is selected from the group consisting of lactose monohydrate, anhydrous lactose, sucrose, mannitol and trehalose.

[14] When the solid carrier comprises lactose it may be in the α- form, the β- form, or a mixture thereof, and may preferably be crystalline.

[15] When the solid carrier comprises lactose it may be in the monohydrate or anhydrous form.

[16] In embodiments, the solid carrier is a powdered solid carrier.

[17] In embodiments, the inhalable formulation of the first aspect is a dry powder inhalable formulation.

[18] In embodiments of the first aspect, the inhalable formulation or dry powder inhalable formulation consists of or consists essentially of a pharmaceutically acceptable salt of epinephrine or an epinephrine derivative, and a solid carrier.

[19] In a preferred embodiment, the inhalable formulation does not comprise any excipients other than the solid carrier. That is, the formulation only contains the epinephrine salt or epinephrine derivative salt and a single solid carrier.

[20] In a second aspect, the disclosure resides in a container comprising the inhalable formulation of the first aspect.

[21] The container may be a capsule, a cartridge, a blister, a blister strip, or other suitable container which, when filled with the formulation of the first aspect, can be loaded into a dry powder inhaler.

[22] In a third aspect, the disclosure resides in a dry powder inhaler comprising the inhalable formulation of the first aspect.

[23] In embodiments, the dry powder inhaler of the second aspect may be as described in any embodiment disclosed in WO2020/257845 and/or WO2020/257843, which are hereby incorporated by reference in their entirety.

[24] In a fourth aspect, the disclosure resides in a process of forming the inhalable formulation of the first aspect, including the steps of:

(a) micronizing a pharmaceutically acceptable salt of epinephrine or an epinephrine derivative, and

(b) combining the micronized pharmaceutically acceptable salt of epinephrine or an epinephrine derivative, with a solid carrier.

[25] In a fifth aspect, the disclosure resides in the inhalable formulation of the first aspect, when produced by the process of the fourth aspect.

[26] In a sixth aspect, the disclosure resides in a method of delivering a pharmaceutically acceptable salt of epinephrine or an epinephrine derivative, to a subject in need thereof, including the step of:

administering the inhalable formulation of the first aspect to the subject,

to thereby deliver the pharmaceutically acceptable salt of epinephrine or the epinephrine derivative, to the subject.

[27] In embodiments, the method of delivering the pharmaceutically acceptable salt of epinephrine or the epinephrine derivative, to the subject includes the steps of:

providing the inhalable formulation of the first aspect to the subject; and

allowing the subject to inhale the inhalable formulation,

to thereby deliver the pharmaceutically acceptable salt of epinephrine or the epinephrine derivative, to the subject.

[28] In embodiments, the step of providing the inhalable formulation of the first aspect may include providing the dry powder inhaler of the third aspect to the subject.

[29] In embodiments, the step of providing the inhalable formulation of the first aspect may include at least partially filling a container with the inhalable formulation.

[30] In embodiments, the method of delivering the pharmaceutically acceptable salt of epinephrine or the epinephrine derivative to a subject further includes the step of loading the container into the dry powder inhaler of the third aspect.

[31] In embodiments, the method of delivering the pharmaceutically acceptable salt of epinephrine or the epinephrine derivative, to a subject is a method of delivering the pharmaceutically acceptable salt of epinephrine or the epinephrine derivative, to the lungs of a subject.

[32] In a seventh aspect, the disclosure resides in a method of preventing or treating a disease, disorder or condition responsive to epinephrine, in a subject in need thereof, including the step of:

administering the inhalable formulation of the first aspect to the subject;

to thereby prevent or treat the disease, disorder or condition in the subject.

[33] In embodiments, the disease, disorder or condition responsive to epinephrine is selected from the group consisting of anaphylaxis, cardiac arrest, glaucoma, asthma, bronchospasm, croup, and respiratory distress.

[34] In embodiments, the method of the seventh aspect includes the steps of:

providing the inhalable formulation of the first aspect to the subject; and

allowing the subject to inhale the inhalable formulation,

to thereby treat the disease or condition in the subject.

[35] In embodiments, the step of providing the inhalable formulation of the first aspect may include providing the dry powder inhaler of the third aspect to the subject.

[36] In embodiments, the method of the seventh aspect further includes the steps of: (i) monitoring the patient; and (ii) optionally administering further amounts of the inhalable formulation of the first aspect.

[37] Each aspect or embodiment as defined herein may be combined with any other aspect(s) or embodiment(s) unless clearly indicated otherwise.

Brief Description of Drawings

[38] Figure 1: shows a SEM (scanning electron microscope) image of the particle size distribution of micronized epinephrine bitartrate at an initial time point.

[39] Figure 2: shows a SEM image of the particle size distribution of micronized epinephrine bitartrate at the 4 week time point (2-8°C).

[40] Figure 3: shows a SEM image of the particle size distribution of micronized epinephrine bitartrate at the 4 week time point (40°C/75%RH).

[41] Figure 4: shows a SEM image of the particle size distribution of micronized epinephrine bitartrate and magnesium stearate at an initial time point.

[42] Figure 5: shows a SEM image of the particle size distribution of micronized epinephrine bitartrate and magnesium stearate at the 4 week time point (2-8°C).

[43] Figure 6: shows a SEM image of the particle size distribution of micronized epinephrine bitartrate and magnesium stearate at the 4 week time point (40°C/75%RH).

[44] Figure 7: shows that the epinephrine formulation with lactose monohydrate pre- and post-blending is free from loose agglomerates.

[45] Figure 8: shows that the epinephrine formulation with lactose monohydrate and magnesium stearate pre- and post-blending is free from loose agglomerates.

[46] Figure 9: is a graphical representation of the NGI testing for Batch BN021/21 1.0 mg strength capsules which had been stored at 25°C/60% RH for 18 months.

Description of Embodiments

[47] It is to be understood that the formulation of the present invention comprising the components as described herein may, in another embodiment, consist of those components, or in another embodiment, consist essentially of those components. In some embodiments, the term "comprise" refers to the inclusion of the indicated components, such as epinephrine and a solid carrier, as well as the inclusion of other components, active agents, and pharmaceutically or physiologically acceptable carriers, excipients, emollients, stabilisers, etc., as are known in the industry. The term "consisting essentially of" refers to a formulation whose only main components are the recited components and

the formulation excludes all further components that will materially affect the essential characteristics of the formulation. However, other compounds may be included which are not involved directly in giving the formulation the desired characteristics of the formulation. The term "consisting of", as used herein, means the formulation includes only the components specifically recited.

[48] The term "substantially" as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art, and refers without limitation to being largely but not necessarily wholly that which is specified. Substantially may mean that something is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, 99.99%, 99.999%, or 99.9999% of that which is specified. For example, "substantially crystalline" can mean that a substance is 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.1%, 99.2%, 99.3%, 99.4%, 99.5%, 99.6%, 99.7%, 99.8%, 99.9%, 99.99%, 99.999%, or 99.9999% crystalline.

[49] As used herein, the term "about" refers to a range of ± 10% of the specified value or a range associated with the experimental error known to the skilled addressee in measuring the specified value, whichever is the greater.

[50] It will be appreciated by the person of skill in the art that epinephrine and adrenaline are two accepted terms for the same active pharmaceutical ingredient (API) and references herein to epinephrine can be considered references to adrenaline. That is, the terms may be used interchangeably herein. Further the term epinephrine may refer to a single pure enantiomer of epinephrine, such as *R*-epinephrine, or racemic epinephrine (containing 1:1 proportions of the *R*- and *S*- enantiomers), or mixtures of any ratio of the enantiomers of epinephrine.

[51] The present disclosure describes how an inhalable epinephrine salt formulation can be uniquely tailored for delivery via a dry powder inhaler (DPI) to a subject's lungs to treat or prevent a condition, disorder or disease responsive to epinephrine. It has been surprisingly found that a simple formulation of a pharmaceutically acceptable salt of epinephrine or of an epinephrine derivative with a solid carrier provides for a stable composition, with useful aerodynamic particle size distribution characteristics, without

the requirement for further force control, lubricating, flow or other agents or excipients. Further, the use of fines of the carrier (e.g., lactose fines) to assist in the deagglomeration of epinephrine bitartrate from alpha lactose monohydrate was found not to be necessary to achieve an aerodynamic particle size distribution useful for inhalation delivery of epinephrine.

[52] In a first aspect, the disclosure resides in an inhalable formulation comprising:

(i) a pharmaceutically acceptable salt of epinephrine, or an epinephrine derivative ; and

(ii) a solid carrier.

[53] In embodiments, the pharmaceutically acceptable salt of epinephrine, or derivative thereof, is a crystalline salt of epinephrine, or derivative thereof.

[54] In embodiments, the pharmaceutically acceptable salt of epinephrine, or derivative thereof, is a crystalline salt of epinephrine.

[55] In embodiments, the pharmaceutically acceptable salt of epinephrine, or derivative thereof, is present within the inhalable formulation at between about 0.01 to about 15.0 mg per unit dose of the formulation. For example, a unit dose of the formulation of the first aspect may comprise the epinephrine salt or epinephrine derivative salt, at between about 0.01 to about 14.0 mg, between about 0.01 to about 13.0 mg, between about 0.01 to about 12.0 mg, between about 0.01 to about 11.0 mg, between about 0.01 to about 10.0 mg, between about 0.01 to about 9.0 mg, between about 0.01 to about 8.0 mg, between about 0.01 to about 7.0 mg, between about 0.01 to about 6.0 mg, between about 0.01 to about 5.0 mg, between about 0.01 to about 4.5 mg, between about 0.01 to about 4.0 mg, between about 0.01 to about 3.5 mg, between about 0.01 to about 3.0 mg, or at between about 0.025 to about 15.0 mg, at between about 0.025 to about 14.0 mg, at between about 0.025 to about 13.0 mg, at between about 0.025 to about 12.0 mg, at between about 0.025 to about 11.0 mg, at between about 0.025 to about 10.0 mg, at between about 0.025 to about 9.0 mg, at between about 0.025 to about 8.0 mg, at between about 0.025 to about 7.0 mg, at between about 0.025 to about 6.0 mg, at between about 0.025 to about 5.0 mg, between about 0.025 to about 4.5 mg, between about 0.025 to about 4.0 mg, between about 0.025 to about 3.5 mg, between about 0.025 to about 3.0

mg, or at between about 0.05 to about 15.0 mg, at between about 0.05 to about 14.0 mg, at between about 0.05 to about 13.0 mg, at between about 0.05 to about 12.0 mg, at between about 0.05 to about 11.0 mg, at between about 0.05 to about 10.0 mg, at between about 0.05 to about 9.0 mg, at between about 0.05 to about 8.0 mg, at between about 0.05 to about 7.0 mg, at between about 0.05 to about 6.0 mg, at between about 0.05 to about 5.0 mg, between about 0.05 to about 4.5 mg, between about 0.05 to about 4.0 mg, between about 0.05 to about 3.5 mg, between about 0.05 to about 3.0 mg, or at between about 0.1 to about 15.0 mg, at between about 0.1 to about 14.0 mg, at between about 0.1 to about 13.0 mg, at between about 0.1 to about 12.0 mg, at between about 0.1 to about 11.0 mg, at between about 0.1 to about 10.0 mg, at between about 0.1 to about 9.0 mg, at between about 0.1 to about 8.0 mg, at between about 0.1 to about 7.0 mg, at between about 0.1 to about 6.0 mg, at between about 0.1 to about 5.0 mg, between about 0.1 to about 4.5 mg, between about 0.1 to about 4.0 mg, between about 0.1 to about 3.5 mg, between about 0.1 to about 3.0 mg, or at between about 0.25 to about 15.0 mg, at between about 0.25 to about 14.0 mg, at between about 0.25 to about 13.0 mg, at between about 0.25 to about 12.0 mg, at between about 0.25 to about 11.0 mg, at between about 0.25 to about 10.0 mg, at between about 0.25 to about 9.0 mg, at between about 0.25 to about 8.0 mg, at between about 0.25 to about 7.0 mg, at between about 0.25 to about 6.0 mg, at between about 0.25 to about 5.0 mg, between about 0.25 to about 4.5 mg, between about 0.25 to about 4.0 mg, between about 0.25 to about 3.5 mg, between about 0.25 to about 3.0 mg, or at between about 0.3 to about 15.0 mg, at between about 0.3 to about 14.0 mg, at between about 0.3 to about 13.0 mg, at between about 0.3 to about 12.0 mg, at between about 0.3 to about 11.0 mg, at between about 0.3 to about 10.0 mg, at between about 0.3 to about 9.0 mg, at between about 0.3 to about 8.0 mg, at between about 0.3 to about 7.0 mg, at between about 0.3 to about 6.0 mg, at between about 0.3 to about 5.0 mg, between about 0.3 to about 4.5 mg, between about 0.3 to about 4.0 mg, between about 0.3 to about 3.5 mg, between about 0.3 to about 3.0 mg, or at between about 0.5 to about 15.0 mg, at between about 0.5 to about 14.0 mg, at between about 0.5 to about 13.0 mg, at between about 0.5 to about 12.0 mg, at between about 0.5 to about 11.0 mg, at between about 0.5 to about 10.0 mg, at between about 0.5 to about 9.0 mg, at between about 0.5 to about 8.0 mg, at between about 0.5 to about 7.0 mg, at between about 0.5 to

about 6.0 mg, at between about 0.5 to about 5.0 mg, between about 0.5 to about 4.5 mg, between about 0.5 to about 4.0 mg, between about 0.5 to about 3.5 mg, between about 0.5 to about 3.0 mg.

[56] It will be appreciated by a person of skill in the art that the unit dose of the epinephrine salt or epinephrine derivative salt, will be determined by the end application. For example, in the treatment of asthma, using the inhalable formulation of the first aspect at a dose of approximately 0.05 to 0.1 mg epinephrine may be sufficient when appropriately delivered. For use in treating anaphylaxis the required dose may be between about 0.1 to 1.0 mg for some pediatric use or between about 1.0 to 2.0 mg for some adult treatment dosage ranges. These factors along with typical therapeutic dosing considerations such as the subject's age, weight and general health would be considered by a skilled formulator or physician and the dose selected accordingly.

[57] It will be appreciated by a person of skill in the art that a much higher dose of the inhalable formulation of the first aspect may be used when treating anaphylactic shock in a patient. The dose may be between about 1.0 to 15.0 mg, or between about 3.0 to 15.0 mg, or between about 5.0 to 15.0 mg. It may be even necessary to give one or more further doses of the inhalable formulation of the first aspect.

[58] In embodiments, the epinephrine salt or epinephrine derivative salt is selected from the group consisting of the bitartrate, hydrochloride, maleate, malate, malonate, fumarate, and borate salts, and mixtures thereof. In an embodiment, the epinephrine salt or epinephrine derivative salt is the bitartrate salt. In a preferred embodiment, the epinephrine salt is epinephrine bitartrate.

[59] It has been found that a salt form of epinephrine can provide significant advantages in stability of the formulation over the free base form of epinephrine.

[60] In embodiments, the epinephrine derivative salt is selected from the group consisting of a norepinephrine salt, a dopamine salt, a 3-methoxytyramine salt, a synephrine salt, a *p*-octopamine salt and mixtures thereof.

[61] In preferred embodiments, the pharmaceutically acceptable salt of epinephrine, or a derivative thereof, is a pharmaceutically acceptable salt of epinephrine. However, it will be appreciated that certain derivatives of epinephrine, or salts thereof, may be

present as impurities or even degradation products which will not negatively impact upon the efficacy of the inhalable formulation to any significant degree. For example, norepinephrine may be present in the formulation at less than about 2.5% w/w, or less than about 1.5% w/w, or less than about 1.0% w/w, or less than about 0.5% w/w.

[62] In embodiments, the solid carrier is present within the inhalable formulation of the first aspect at between 25% w/w to 99% w/w of the entire formulation. For example, the formulation of the first aspect may comprise a solid carrier at between 30% w/w to 99% w/w, or at between 35% w/w to 99% w/w, or at between 40% w/w to 99% w/w, or at between 45% w/w to 99% w/w, or at between 50% w/w to 99% w/w, or at between 55% w/w to 99% w/w, at between 60% w/w to 99% w/w, or at between 65% w/w to 99% w/w, or at between 70% w/w to 99% w/w, or at between 75% w/w to 99% w/w, or at between 80% w/w to 99% w/w, or at between 85% w/w to 99% w/w, or at between 30% w/w to 98% w/w, or at between 35% w/w to 98% w/w, or at between 40% w/w to 98% w/w, or at between 45% w/w to 98% w/w, or at between 50% w/w to 98% w/w, or at between 55% w/w to 98% w/w, or at between 60% w/w to 98% w/w, or at between 65% w/w to 98% w/w, or at between 70% w/w to 98% w/w, or at between 75% w/w to 98% w/w, or at between 80% w/w to 98% w/w, or at between 85% w/w to 98% w/w, or at between 30% w/w to 97% w/w, or at between 35% w/w to 97% w/w, or at between 40% w/w to 97% w/w, or at between 45% w/w to 97% w/w, or at between 50% w/w to 97% w/w, or at between 55% w/w to 97% w/w, or at between 60% w/w to 97% w/w, or at between 65% w/w to 97% w/w, or at between 70% w/w to 97% w/w, or at between 75% w/w to 97% w/w, or at between 80% w/w to 97% w/w, or at between 85% w/w to 97% w/w, or at between 30% w/w to 96% w/w, or at between 35% w/w to 96% w/w, or at between 40% w/w to 96% w/w, or at between 45% w/w to 96% w/w, or at between 50% w/w to 96% w/w, or at between 55% w/w to 96% w/w, or at between 60% w/w to 96% w/w, or at between 65% w/w to 96% w/w, or at between 70% w/w to 96% w/w, or at between 75% w/w to 96% w/w, or at between 80% w/w to 96% w/w, or at between 85% w/w to 96% w/w, or at between 30% w/w to 95% w/w, or at between 35% w/w to 95% w/w, or at between 40% w/w to 95% w/w, or at between 45% w/w to 95% w/w, or at between 50% w/w to 95% w/w, or at between 55% w/w to 95% w/w, or at between 60% w/w to 95% w/w, or at between 65% w/w to 95% w/w, or at between 70% w/w to 95%

w/w, or at between 75% w/w to 95% w/w, or at between 80% w/w to 95% w/w, or at between 85% w/w to 95% w/w.

[63] In embodiments, the solid carrier is present within the inhalable formulation of the first aspect at between 85% w/w to 95% w/w, or at between 85% w/w to 94% w/w, or at between 85% w/w to 93% w/w, or at between 85% w/w to 92% w/w, or at between 86% w/w to 95% w/w, or at between 86% w/w to 94% w/w, or at between 86% w/w to 93% w/w, or at between 86% w/w to 92% w/w, or at between 87% w/w to 95% w/w, or at between 87% w/w to 94% w/w, or at between 87% w/w to 93% w/w, or at between 87% w/w to 92% w/w, or at between 88% w/w to 95% w/w, or at between 88% w/w to 94% w/w, or at between 88% w/w to 93% w/w, or at between 88% w/w to 92% w/w.

[64] In another preferred embodiment, when the inhalable formulation is directed to pediatric use, the solid carrier may be present within the inhalable formulation of the first aspect at between 90% w/w to 99% w/w, or at between 90% w/w to 98% w/w, or at between 90% w/w to 97% w/w, or at between 90% w/w to 96% w/w, or at between 91% w/w to 99% w/w, or at between 91% w/w to 98% w/w, or at between 91% w/w to 97% w/w, or at between 91% w/w to 96% w/w, or at between 92% w/w to 99% w/w, or at between 92% w/w to 98% w/w, or at between 92% w/w to 97% w/w, or at between 92% w/w to 96% w/w, or at between 93% w/w to 99% w/w, or at between 93% w/w to 98% w/w, or at between 93% w/w to 97% w/w, or at between 93% w/w to 96% w/w, or at between 94% w/w to 99% w/w, or at between 94% w/w to 98% w/w, or at between 94% w/w to 97% w/w, or at between 94% w/w to 96% w/w.

[65] In a preferred embodiment, when the solid carrier of the inhalable formulation of any embodiment of the first aspect is a lactose monohydrate and/or an anhydrous lactose solid carrier, optionally a crystalline lactose monohydrate and/or a crystalline anhydrous lactose, the lactose monohydrate and/or the anhydrous lactose solid carrier is present within the inhalable formulation of the first aspect at between 25% w/w to 99% w/w, or at between 30% w/w to 99% w/w, or at between 35% w/w to 99% w/w, or at between 40% w/w to 99% w/w, or at between 45% w/w to 99% w/w, or at between 50% w/w to 99% w/w, or at between 55% w/w to 99% w/w, or at between 60% w/w to 99% w/w, or at between 65% w/w to 99% w/w, or at between 70% w/w to 99% w/w, or at between 75% w/w to 99% w/w, or at between 80% w/w to 99% w/w, or at between 85%

w/w to 99% w/w, or at between 30% w/w to 98% w/w, or at between 35% w/w to 98% w/w, or at between 40% w/w to 98% w/w, or at between 45% w/w to 98% w/w, or at between 50% w/w to 98% w/w, or at between 55% w/w to 98% w/w, or at between 60% w/w to 98% w/w, or at between 65% w/w to 98% w/w, or at between 70% w/w to 98% w/w, or at between 75% w/w to 98% w/w, or at between 80% w/w to 98% w/w, or at between 85% w/w to 98% w/w, or at between 30% w/w to 97% w/w, or at between 35% w/w to 97% w/w, or at between 40% w/w to 97% w/w, or at between 45% w/w to 97% w/w, or at between 50% w/w to 97% w/w, or at between 55% w/w to 97% w/w, or at between 60% w/w to 97% w/w, or at between 65% w/w to 97% w/w, or at between 70% w/w to 97% w/w, or at between 75% w/w to 97% w/w, or at between 80% w/w to 97% w/w, or at between 85% w/w to 97% w/w, or at between 30% w/w to 96% w/w, or at between 35% w/w to 96% w/w, or at between 40% w/w to 96% w/w, or at between 45% w/w to 96% w/w, or at between 50% w/w to 96% w/w, or at between 55% w/w to 96% w/w, or at between 60% w/w to 96% w/w, or at between 65% w/w to 96% w/w, or at between 70% w/w to 96% w/w, or at between 75% w/w to 96% w/w, or at between 80% w/w to 96% w/w, or at between 85% w/w to 96% w/w, or at between 30% w/w to 95% w/w, or at between 35% w/w to 95% w/w, or at between 40% w/w to 95% w/w, or at between 45% w/w to 95% w/w, or at between 50% w/w to 95% w/w, or at between 55% w/w to 95% w/w, or at between 60% w/w to 95% w/w, or at between 65% w/w to 95% w/w, or at between 70% w/w to 95% w/w, or at between 75% w/w to 95% w/w, or at between 80% w/w to 95% w/w, or at between 85% w/w to 95% w/w. In another preferred embodiment, the lactose monohydrate and/or the anhydrous lactose solid carrier is present within the inhalable formulation of the first aspect at between 85% w/w to 95% w/w, or at between 85% w/w to 94% w/w, or at between 85% w/w to 93% w/w, or at between 85% w/w to 92% w/w, or at between 86% w/w to 95% w/w, or at between 86% w/w to 94% w/w, or at between 86% w/w to 93% w/w, or at between 86% w/w to 92% w/w, or at between 87% w/w to 95% w/w, or at between 87% w/w to 94% w/w, or at between 87% w/w to 93% w/w, or at between 87% w/w to 92% w/w, or at between 88% w/w to 95% w/w, or at between 88% w/w to 94% w/w, or at between 88% w/w to 93% w/w, or at between 88% w/w to 92% w/w.

[66] In another preferred embodiment, when the inhalable formulation is directed to pediatric use, the lactose monohydrate and/or the anhydrous lactose solid carrier may be present within the inhalable formulation of the first aspect at between 90% w/w to 99% w/w, or at between 90% w/w to 98% w/w, or at between 90% w/w to 97% w/w, or at between 90% w/w to 96% w/w, or at between 91% w/w to 99% w/w, or at between 91% w/w to 98% w/w, or at between 91% w/w to 97% w/w, or at between 91% w/w to 96% w/w, or at between 92% w/w to 99% w/w, or at between 92% w/w to 98% w/w, or at between 92% w/w to 97% w/w, or at between 92% w/w to 96% w/w, or at between 93% w/w to 99% w/w, or at between 93% w/w to 98% w/w, or at between 93% w/w to 97% w/w, or at between 93% w/w to 96% w/w, or at between 94% w/w to 99% w/w, or at between 94% w/w to 98% w/w, or at between 94% w/w to 97% w/w, or at between 94% w/w to 96% w/w.

[67] The aerodynamic particle size distribution is a key parameter to consider to ensure delivery of the inhalable formulation to the deep lungs. Particles with diameters greater than 5 μm generally deposit in the mouth, throat or upper airways whereas articles with a diameter of less than 0.5 μm do not settle out of the airflow to deposit in the lungs, and are subsequently exhaled immediately. It has been advantageously found that the inhalable formulations of the present disclosure provide for a useful particle size profile for delivery of the epinephrine active to the lung.

[68] In embodiments, the median particle size distribution by volume (Dv50) of the epinephrine salt or epinephrine derivative salt, is between about 0.5 μm to about 5 μm. In an embodiment, the Dv50 value of the epinephrine salt or epinephrine derivative salt, is between 1 μm to about 4 μm, or between 1 μm to about 3 μm, or between 2 μm to about 3 μm.

[69] In another embodiment, the maximum particle diameter below which 90% of the epinephrine salt or epinephrine derivative salt, exists (Dv90) is between about 2 μm to about 5 μm. In an embodiment, the Dv90 value of the epinephrine salt or epinephrine derivative salt, is between 3 μm to about 4 μm.

[70] A range of solid carriers suitable to inhalation formulations are known in the art. In embodiments, the solid carrier may be selected from the group consisting of

sugars, sugar alcohols, citrates, amino acids and peptides, vitamins and other suitable solid carriers.

[71] When the solid carrier is a sugar or sugar alcohol, it may be selected from the group consisting of lactose, mannose, sucrose, mannitol and trehalose.

[72] When the solid carrier is a citrate it may be selected from the group consisting of zinc citrate and trisodium citrate.

[73] When the solid carrier is an amino acid or peptide it may be selected from the group consisting of glycine, L-leucine, isoleucine, methionine and trileucine.

[74] When the solid carrier is a vitamin it may be vitamin A.

[75] Other suitable carriers may include zinc chloride, polyvinylpyrrolidone, and diphosphotidylcholine and the like.

[76] In an embodiment, the solid carrier is selected from the group consisting of alpha-lactose monohydrate, beta-lactose, anhydrous lactose, mannitol, sucrose, and trehalose.

[77] When the solid carrier comprises lactose it may be in the α-form, the β-form, or a mixture thereof, and may be crystalline in either form.

[78] It will be appreciated by a person of skill in the art that the α-lactose form can exist as both a monohydrate and an anhydrous form. Further, the β-form generally exists as an anhydrous form only, not a hydrate. When the solid carrier comprises lactose it may be in any of these forms both singularly and in any combination. For example, the solid carrier may comprise α-lactose in both monohydrate and anhydrous forms with or without the anhydrous β-form being present. In combination with all of these embodiments of α- and/or β-lactose, the lactose may be in crystalline or amorphous forms. It may be preferred that any α- and/or β-lactose forms are crystalline.

[79] In embodiments, the solid carrier is a powdered solid carrier.

[80] The solid carrier, optionally lactose solid carrier, may have a particle size distribution as follows: D10 between 20 to 45 μm, optionally between 25 to 35 μm; D50 between 50 to 70 μm, optionally between 55 to 65 μm; and D90 between 75 to 105 μm, optionally between 85 to 100 μm. In embodiments the solid carrier is the commercially

available Respitose SV003 provided by DFE Pharma, although similar grades of lactose solid carrier would also be suitable.

[81] In preferred embodiments of the first aspect, the solid carrier comprises or consists of or consists essentially of a crystalline solid carrier.

[82] In embodiments, the majority of the solid carrier is in crystalline form. Crystalline carriers are preferable for the present inhalable formulation as they reduce processing complexity and are thermodynamically more stable than amorphous carriers. The use of a crystalline sold carrier means there is no need for a pharmaceutical spray dryer, the solid carrier is therefore not constrained to spray drying amenable materials only, the stability thermodynamics may be improved in the crystalline state, and the crystalline epinephrine salt may be less hygroscopic than amorphous epinephrine salt forms.

[83] In embodiments, the inhalable formulation of the first aspect is a dry powder inhalable formulation. That is, all of the components of the formulation for delivery to a subject are in a substantially dry powder form.

[84] In embodiments of the first aspect, the solid carrier consists or consists essentially of lactose monohydrate and/or anhydrous lactose, optionally crystalline lactose monohydrate and/or crystalline anhydrous lactose.

[85] In certain examples, the dry powder inhalable formulation comprises, consists or consists essentially of:

(i) a pharmaceutically acceptable salt of epinephrine, optionally the bitartrate salt of epinephrine; and

(ii) a lactose-based solid carrier, optionally a lactose monohydrate and/or an anhydrous lactose solid carrier, optionally a crystalline lactose monohydrate and/or a crystalline anhydrous lactose.

[86] In certain examples, the dry powder inhalable formulation comprises, consists or consists essentially of:

(i) a pharmaceutically acceptable salt of epinephrine, optionally the bitartrate salt of epinephrine; and

(ii) a lactose-based solid carrier, optionally a lactose monohydrate and/or an anhydrous lactose solid carrier, optionally a crystalline lactose monohydrate and/or a crystalline anhydrous lactose, wherein the lactose-based solid carrier is present at between about 50% w/w to about 99% w/w.

[87] The epinephrine salt and lactose carrier may be as described in any previous embodiment or combination thereof.

[88] In embodiments of the first aspect, the inhalable formulation or dry powder inhalable formulation consists of or consists essentially of an epinephrine salt or epinephrine derivative salt; and a solid carrier.

[89] Typically, a number of other excipients and carriers have to be added to dry powder formulations to achieve the desired properties, such as desired stability of the formulation, the right aerodynamic particle size distribution and the necessary anti-agglomeration properties of the particles. This may be particularly so for epinephrine which can be challenging to formulate while maintaining stability, preventing reactions with one or more of the formulation components and avoiding significant agglomeration and clumping of the formulation. It has surprisingly been found that it is not necessary to add any further excipients other than the chosen solid carrier to the pharmaceutically acceptable epinephrine salt to form the inhalable formulation of the present disclosure and to achieve the described benefits. Further, it was not necessary to add a fines fraction of the carrier excipient to assist the de-agglomeration of API from carrier particles. The inhalable formulation described herein therefore does not require a delivery device which has been particularly designed with a focus on achieving deagglomeration of clumps of dry powder. Such devices can be complex, require expensive manufacturing and may often not be successful in the deagglomeration process thereby resulting in poor delivery of the active agent. The simplicity of the inhalable formulation described herein is a significant advantage of the present invention while maintaining the described advantages.

[90] In embodiments of the first aspect, the inhalable formulation does not comprise any agent which could be considered to be or which plays an active role as an excipient, a second carrier material, a flow control agent, a lubricant, a force control agent, a pH

buffering agent, or other additive which assists in delivery of the active epinephrine form, other than the recited solid carrier.

[91] In any embodiment of the present disclosure, the inhalable formulation of the first aspect does not comprise a pH buffering agent, such as sodium dihydrogen phosphate. While a buffering agent may be required for formulations to be delivered intranasally they are not required for the present formulation which is designed for delivery to the lungs via a DPI.

[92] Therefore, when the inhalable formulation of the first aspect comprises epinephrine bitartrate and lactose monohydrate it does not comprise sodium dihydrogen phosphate.

[93] Therefore, in examples, the inhalable formulation of the first aspect comprises: (i) a pharmaceutically acceptable epinephrine salt or epinephrine derivative salt, optionally epinephrine bitartrate; and (ii) a single excipient which is a solid carrier. Optionally, the single excipient which is a solid carrier is a lactose carrier such as lactose monohydrate and/or an anhydrous lactose. The lactose carrier may comprise any ratio of α- and β-lactose forms and may be crystalline, amorphous or a mixture thereof. Crystalline lactose forms may, in certain examples, be preferred.

[94] In embodiments, the inhalable formulation comprises: (i) a pharmaceutically acceptable salt of epinephrine or of an epinephrine derivative, optionally epinephrine bitartrate; and (ii) lactose monohydrate and/or an anhydrous lactose.

[95] In any embodiment of the first aspect, the epinephrine salt or epinephrine derivative salt is crystalline micronized epinephrine bitartrate.

[96] In an embodiment of the first aspect, the inhalable formulation comprises, consists essentially of or consists of: (i) micronized epinephrine bitartrate; and (ii) a crystalline lactose solid carrier present at between about 50% w/w to about 99% w/w of the entire formulation and which is selected from a lactose monohydrate solid carrier and/or an anhydrous lactose solid carrier.

[97] In embodiments, the crystalline lactose solid carrier is present at between 55% w/w to 99% w/w, or at between 60% w/w to 99% w/w, or at between 65% w/w to 99%

w/w, or at between 70% w/w to 99% w/w, or at between 75% w/w to 99% w/w, or at between 80% w/w to 99% w/w, or at between 85% w/w to 99% w/w.

[98] In an embodiment of the first aspect, the inhalable formulation comprises, consists essentially of or consists of: (i) micronized epinephrine bitartrate having a Dv50 of between about 0.5 μm to about 5 μm and/or a Dv90 of between about 2 μm to about 5 μm; and (i) a solid carrier, optionally a lactose solid carrier such as lactose monohydrate and/or an anhydrous lactose.

[99] In an embodiment of the first aspect, the inhalable formulation comprises, consists essentially of or consists of: (i) micronized epinephrine bitartrate having a Dv50 of between about 0.5 μm to about 5 μm and a Dv90 of between about 2 μm to about 5 μm; and (i) a solid carrier, optionally a lactose solid carrier such as lactose monohydrate and/or an anhydrous lactose.

[100] In embodiments, the Dv50 is between about 1 μm to about 5 μm, or between about 1 μm to about 4 μm, or between about 1 μm to about 3 μm, or between about 1 μm to about 2 μm, or between about 1.5 μm to about 5 μm, or between about 1.5 μm to about 4 μm, or between about 1.5 μm to about 3 μm, or between about 1.5 μm to about 2 μm, or between about 2 μm to about 5 μm, or between about 2 μm to about 4 μm, or between about 2 μm to about 3 μm.

[101] In an embodiment, the Dv50 is between about 1.5 μm to about 3 μm.

[102] In an embodiment, the Dv50 is about 2 μm.

[103] In embodiments, the Dv90 is between about 2 μm to about 4.5 μm, or between about 2 μm to about 4 μm, or between about 2.5 μm to about 5 μm, or between about 2.5 μm to about 4.5 μm, or between about 2.5 μm to about 4 μm, between about 3 μm to about 5 μm, between about 3 μm to about 4.5 μm, or between 3 μm to about 4 μm. In embodiments, the inhalable formulation provides for a fine particle fraction, expressed as a percentage of the fine particle dose relative to the emitted dose, of greater than 20%, or greater than 25%, or greater than 30%, or greater than 35%, or greater than 40%.

[104] In embodiments, the crystalline micronized epinephrine bitartrate has not been formed by a spray drying process.

[105] The combination of epinephrine with lactose has been found to be especially advantageous as an inhalable formulation. Epinephrine powder alone was found to have a strong tendency to agglomerate. This is a major risk factor for a dry powder inhaler formulation since agglomeration of particles greatly increases the particle size and significantly reduces the percentage of the API that is successfully delivered to the deep lung. Particularly, it was found that crystalline micronized epinephrine bitartrate alone would form agglomerates and it was expected that various glidants and/or anti-agglomerating agents would be required in addition to a solid carrier or that complex processing approaches, such as spray drying, would be necessary. As described in the Examples, it has surprisingly been found the inhalable formulation of the present invention shows minimal signs of agglomeration when epinephrine is used purely in combination with a lactose carrier. Therefore, it has been found that the inhalable formulation of the present invention is extremely stable in aerodynamic particle size distribution over an extended period of time and provides for a desirable sustained FPF for delivery to a subject.

[106] As described in the Examples, it has been found that the inhalable formulation comprising an epinephrine salt and lactose is stable for at least 6 months at ambient temperature (25 °C) and at elevated temperatures (40 °C). Additionally, the formulation has been found to be stable at up to 75% relative humidity. Therefore, in embodiments, the inhalable formulation according to the embodiments of the first aspect is stable for storage for at least 3 months, or at least 4 months, or at least 5 months, or at least 6 months, or at least 7 months, or at least 8 months. In embodiments, the inhalable formulation is stable for storage for at least 3 months, or at least 4 months, or at least 5 months, or at least 6 months, or at least 7 months, or at least 8 months when stored at a temperature between about ambient temperature (25 °C) and about 40 °C. In embodiments, the inhalable formulation is stable for storage for at least 3 months, or at least 4 months, or at least 5 months, or at least 6 months, or at least 7 months, or at least 8 months when stored at a temperature between about ambient temperature (25 °C) and about 40 °C and at a relative humidity of between about 60% to 75%.

[107] In an embodiment, the inhalable formulation comprises, consists essentially of or consists of (i) micronized epinephrine bitartrate; and (ii) a lactose solid carrier,

wherein the inhalable formulation is stable for storage for 6 months at about ambient temperature (25 °C) and about 60% relative humidity.

[108] In an embodiment, the inhalable formulation comprises, consists essentially of or consists of (i) micronized crystalline epinephrine bitartrate having a Dv50 of between about 1.5 μm to about 3 μm and a Dv90 of between about 2 μm to about 5 μm; and (ii) crystalline α-lactose monohydrate present at between about 75% w/w to about 99% w/w of the entire formulation, wherein the dry powder inhalable formulation: (a) provides for a fine particle fraction, expressed as a percentage of the fine particle dose relative to the emitted dose, of greater than 30% upon manufacture; and/or (b) is stable for storage for 6 months at 25 °C and 60 % relative humidity.

[109] As discussed above, this stability in aerodynamic particle size distribution over an extended period of time is a significant and unexpected advantage in that further processing steps or particular storage processes do not have to be implemented to the extent they would for an inhalable formulation which does tend to naturally agglomerate. Additionally, the inhalable formulation of the first aspect does not require delivery only by specified dry powder inhalers which are designed with component parts or chambers which have a purpose of deagglomerating clumped dry powder formulation. This could not have been expected with an epinephrine formulation when crystalline micronized epinephrine, such as epinephrine bitartrate, is demonstrated to naturally form significant agglomerates. The challenge of avoiding or reducing epinephrine agglomeration could further not have been expected to be solved by a single carrier, and particularly by a lactose carrier for reasons further discussed below.

[110] Without wishing to be bound by theory, this unexpected effect may be due to the lactose having an unexpectedly strong stabilizing effect on the epinephrine particle size distribution during long term storage where, otherwise, the epinephrine, particularly epinephrine bitartrate, would readily self-agglomerate and so require further processing prior to loading or specialized equipment for delivery to a subject. This could not have been anticipated and, in fact, quite the opposite would have been expected based on the known reaction between secondary amines, such as epinephrine, and reducing sugars, such as lactose as discussed below.

[111] Challenges to be aware of when creating pharmaceutical formulations include undesired side reactions, such as the Maillard reaction. The Maillard reaction is a chemical reaction between a secondary amine (such as epinephrine) and a reducing sugar (such as lactose). Wirth et al, for example, observed the Maillard reaction for all of their performed experiments using a secondary amine and alpha-lactose monohydrate or anhydrous lactose (Wirth et al., "Maillard Reaction of Lactose and Fluoxetine Hydrochloride, a Secondary Amine", Journal of Pharmaceutical Sciences, Vol 87(1):31-39, January 1998, which is hereby incorporated in its entirety by reference).

[112] This reaction gives a distinct browning color development in the powder as the degradation reaction proceeds and may be problematic with epinephrine formulations. To prevent this reaction, further additives such as antioxidants are usually added. In the food industry, these additives are usually sulfite compounds, such as sulfur dioxide or salts containing metabisulfite, which are known triggers for asthma, even inhaled at low levels. It is therefore particularly surprising that a lactose solid carrier could be used alone with epinephrine bitartrate to solve the above-mentioned problems of agglomeration while not resulting in stability or storage difficulties based on an expected reaction between the two components. The combination of an epinephrine salt with a reducing sugar, as a solid carrier, as the only two components of a formulation would not be a solution which would present itself naturally to a skilled formulator based upon the inherent problems it would be expected to bring about. The present inhalable formulation does not require or comprise an antioxidant.

[113] It may therefore be especially advantageous and surprising that the inhalable formulation of the present invention, particularly when lactose is the solid carrier, does not show any tendency to undergo side reactions. As demonstrated in the Examples, the inhalable formulation has a high chemical stability even after 6 months of storage and shows no signs of Maillard browning degradation despite the lack of an antioxidant excipient. The clumping of epinephrine alone is therefore avoided in the claimed formulation and the expected Maillard reaction is not seen to occur even over extended storage periods.

[114] In embodiments, the inhalable formulation consists of or consists essentially of:

(i) a pharmaceutically acceptable salt of epinephrine or of an epinephrine derivative; and

(ii) lactose monohydrate and/or an anhydrous lactose.

[115] In embodiments, the inhalable formulation consists of or consists essentially of: (i) epinephrine bitartrate; and (ii) α-lactose monohydrate and/or anhydrous α-lactose, optionally the epinephrine bitartrate is crystalline epinephrine bitartrate including micronized crystalline epinephrine bitartrate, optionally the α-lactose monohydrate and/or anhydrous α-lactose are crystalline.

[116] In embodiments, the inhalable formulation does not contain lactose fines in addition to the solid carrier. Lactose fines are milled and micronized lactose particles. They are usually added to a dry powder inhaler formulation as a separate grade of lactose (processed via milling, micronization, sieving, classification, or other means of producing a powder with substantially smaller particle sizes than standard grades of lactose). Lactose fines are added to various pharmaceutical product DPI formulations to help the disagglomeration and dispersion of fine API particles from the solid carrier particles within the aerosol and, therefore, improve the delivery of the API to the deep lungs. While a small amount of lactose fines in the inhalable formulation of the present disclosure may be useful or moderately beneficial, it is an advantage that it is not necessary to add lactose fines to epinephrine DPI formulations of the first aspect to achieve a pharmaceutically useful aerodynamic particle size distribution, flowability, and to minimize aggregation. Surprisingly, the inhalable formulation of the present invention shows the desired delivery properties to the deep lung when regular particle size lactose (Respitose®) is used.

[117] In embodiments when the inhalable formulation comprises lactose fines they are present at less than 20 %w/w, or less than 15 %w/w, or less than 10 %w/w, or less than 5 %w/w, or less than 3 %w/w, or less than 1.5 %w/w of the entire formulation.

[118] In a preferred embodiment, the inhalable formulation does not comprise magnesium stearate. Magnesium stearate is a common lubricant excipient added to dry powder formulations to improve aerosol performance and resistance to moisture. It may be especially advantageous that the inhalable formulation of the present invention does

not need addition of magnesium stearate to show the desired properties. It is generally expected in the field that to achieve a suitable aerodynamic particle size distribution of such epinephrine and solid carrier formulations, a lubricant is required to reduce adherence of the powder formulation to the container and any device surfaces, and to assist in consistent processing of the encapsulation step during manufacture of capsules. It was found that the inhalable formulations of the first aspect do not require this additional functionality of magnesium stearate or any other lubricant in order to satisfy the required parameters and, indeed, may benefit by their absence.

[119] In a second aspect, the disclosure resides in a container comprising the inhalable formulation of the first aspect.

[120] The container may be a capsule, a cartridge, a blister, a blister strip, or other suitable container which, when filled with the formulation of the first aspect, can be loaded into a dry powder inhaler.

[121] Such containers are well-known in the art and will vary depending on the manner in which the formulation is to be released from the container during an inhalation operation using the appropriate delivery device. In one embodiment, the container may be a capsule suitable to be pierced by one or more actuators within the delivery device. The container may be as described in WO2020/257845 and/or WO2020/257843, although it will be appreciated the present invention is not so limited.

[122] In a third aspect, the disclosure resides in a dry powder inhaler comprising the inhalable formulation of the first aspect and/or the container of the second aspect.

[123] In embodiments, the dry powder inhaler of the third aspect may be as described in any embodiment disclosed in WO2020/257845 and/or WO2020/257843, which are hereby incorporated by reference in their entirety.

[124] In embodiments, the inhalable formulation of the first aspect is provided in capsules, as described for the second aspect, that are designed for use in the dry powder inhaler of the third aspect.

[125] In a fourth aspect, the disclosure resides in a process of forming the inhalable formulation of the first aspect, including the steps of:

(a) micronizing the epinephrine salt or epinephrine derivative salt, and

(b) combining the micronized epinephrine salt or epinephrine derivative salt, with the solid carrier.

[126] In embodiments, the step of micronizing the epinephrine salt may be carried out using cryogenic micronization or ambient temperature micronization approaches. It is one advantage of the present disclosure that cryogenic micronization, while useful, is not a requirement to achieve a useful formulation.

[127] In embodiments, the micronized epinephrine salt or epinephrine derivative salt, and the solid carrier are passed through a sieve before being combined.

[128] In embodiments, the combining step is a step of dry blending the solid carrier with the micronized epinephrine salt or epinephrine derivative salt.

[129] In embodiments, the median particle size distribution (Dv50) of the epinephrine salt or epinephrine derivative salt, is between about 0.5 μm to about 5 μm, or between about 1 μm to about 5 μm, or between about 1 μm to about 4 μm, or between about 1 μm to about 3 μm, or between about 1 μm to about 2 μm, or between about 1.5 μm to about 5 μm, or between about 1.5 μm to about 4 μm, or between about 1.5 μm to about 3 μm, or between about 1.5 μm to about 2 μm, or between about 2 μm to about 5 μm, or between about 2 μm to about 4 μm, or between about 2 μm to about 3 μm after micronization.

[130] In an embodiment, the median particle size distribution (Dv50) of the epinephrine salt or epinephrine derivative salt, is between about 1.5 μm to about 3 μm. In embodiments, the median particle size distribution (Dv50) of the epinephrine salt or epinephrine derivative salt, is about 2.0 μm. It has been advantageously found that this particle size distribution can be maintained in storage stably for at least a period of one month.

[131] In embodiments, the inhalable formulation of the first aspect can be blended by either low shear or high shear blending techniques. It is an advantage of the formulation of the first aspect that the requirements are very low in terms of the need for tight processing controls of any critical process parameters in the intensity or time of blending. This affords a robust process that can be more readily scaled-up compared to a process

that may have more process parameter criticality or sensitivity over how the API and solid carrier are blended. For example, the process of the fourth aspect does not require a spray drying step.

[132] In embodiments, the process of the fourth aspect further comprises a step of packing the inhalable formulation in suitable containers of the second aspect for use in the dry powder inhaler of the third aspect.

[133] In a fifth aspect, the disclosure resides in the inhalable formulation of the first aspect, when produced by the process of the fourth aspect.

[134] In a sixth aspect, the disclosure resides in a method of delivering the epinephrine salt or epinephrine derivative salt, to a subject in need thereof, including the step of:

administering the inhalable formulation of the first aspect to the subject,

to thereby deliver the epinephrine salt or epinephrine derivative salt, to the subject.

[135] In embodiments, the method of delivering the epinephrine salt or epinephrine derivative salt, to the subject includes the steps of:

providing the inhalable formulation of the first aspect to the subject; and

allowing the subject to inhale the inhalable formulation,

to thereby deliver the epinephrine salt or epinephrine derivative salt, to the subject.

[136] In embodiments, the step of providing the inhalable formulation of the first aspect may include providing the dry powder inhaler of the third aspect to the subject.

[137] In embodiments, the step of providing the inhalable formulation of the first aspect may include at least partially filling a container with the inhalable formulation.

[138] In embodiments, the method of delivering the epinephrine salt or epinephrine derivative salt, to a subject further includes the step of loading the container into the dry powder inhaler of the third aspect.

[139] In embodiments, the method of delivering epinephrine to a subject is a method of delivering epinephrine to the respiratory tract and, particularly, to the lungs of a subject.

[140] It may be especially advantageous to treat a subject with the inhalable formulation of the first aspect. The unique properties of the inhalable formulation, such as the anti-agglomeration properties and the aerodynamic particle size distribution, allow the epinephrine salt or epinephrine derivative salt, to travel to the deep lung through inhalation without depositing in the upper airways and the throat.

[141] In embodiments, the method of delivering epinephrine to a subject is a method of self-administering the inhalable formulation to the respiratory tract by using the dry powder inhaler of the third aspect.

[142] In a seventh aspect, the disclosure resides in a method of treating or preventing a disease, disorder or condition responsive to epinephrine in a subject in need thereof, including the step of:

administering the inhalable formulation of the first aspect to the subject;

to thereby treat or prevent the disease, disorder or condition in the subject.

[143] The unique properties of the inhalable formulation allow the epinephrine salt or epinephrine derivative salt, to reach the deep lung without delay and, therefore, the method of the seventh aspect is a quick and convenient way of treating a disease, disorder or condition responsive to epinephrine.

[144] In embodiments, the disease, disorder or condition responsive to epinephrine is selected from the group consisting of anaphylaxis, cardiac arrest, glaucoma, asthma, bronchospasm, croup, and respiratory distress.

[145] In embodiments, the method of the seventh aspect includes the steps of:

providing the inhalable formulation of the first aspect to the subject; and

allowing the subject to inhale the inhalable formulation,

to thereby treat or prevent the disease, disorder or condition in the subject.

[146] In embodiments, the step of providing the inhalable formulation of the first aspect may include providing the dry powder inhaler of the third aspect to the subject.

[147] In embodiments, the step of allowing the subject to inhale the inhalable formulation includes a substantial proportion of the inhalable formulation reaching the lungs of the subject as a result of the inhalation.

[148] In embodiments, the method of the seventh aspect further includes the steps of: (i) monitoring the patient; and (ii) optionally administering further amounts of the inhalable formulation of the first aspect.

[149] It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the above-described embodiments, without departing from the broad general scope of the present disclosure. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

ITEMISED LISTING OF EMBODIMENTS:

1. An inhalable formulation comprising, consisting of or consisting essentially of:

(i) a pharmaceutically acceptable salt of epinephrine or a pharmaceutically acceptable salt of an epinephrine derivative; and

(ii) a solid carrier.

2. The inhalable formulation of item 1, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative, is present at between about 0.01 to about 5.0 mg per unit dose of the formulation

3. The inhalable formulation of item 1 or item 2, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative, is a salt selected from the group consisting of bitartrate, hydrochloride, maleate, malate, malonate, borate and fumarate.

4. The inhalable formulation of any one of the preceding items, wherein the epinephrine derivative is selected from the group consisting of norepinephrine, dopamine, 3-methoxytyramine, synephrine, *p*-octopamine.

5. The inhalable formulation of any one of the preceding items, wherein the solid carrier is selected from the group consisting of alpha-lactose monohydrate, beta-lactose, an anhydrous lactose, mannitol, sucrose, and trehalose.

6. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation does not comprise any other excipients than the solid carrier.

7. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation does not comprise a pH buffer agent.

8. The inhalable formulation of any one of the preceding items, wherein the solid carrier is a crystalline solid carrier.

9. The inhalable formulation of any one of the preceding items, wherein the epinephrine or epinephrine derivative salt is crystalline.

10. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists or consists essentially of a crystalline epinephrine salt and a crystalline lactose solid carrier.

11. The inhalable formulation of any one of the preceding items, wherein the solid carrier is present within the inhalable formulation at between about 50% w/w to 99% w/w of the entire formulation, optionally at between about 75% w/w to 99% w/w of the entire formulation.

12. The inhalable formulation of any one of the preceding items, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative is a micronized crystalline pharmaceutically acceptable salt of epinephrine or epinephrine derivative.

13. The inhalable formulation of any one of the preceding items, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative is epinephrine bitartrate.

14. The inhalable formulation of any one of the preceding items, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative is crystalline epinephrine bitartrate.

15. The inhalable formulation of any one of the preceding items, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative is micronized crystalline epinephrine bitartrate.

16. The inhalable formulation of any one of the preceding items, wherein the solid carrier is selected from the group consisting of alpha-lactose monohydrate and an anhydrous lactose.

17. The inhalable formulation of any one of the preceding items, wherein the solid carrier is selected from the group consisting of crystalline alpha-lactose monohydrate and a crystalline anhydrous lactose.

18. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of epinephrine bitartrate and a solid carrier.

19. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of crystalline epinephrine bitartrate and a solid carrier.

20. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of crystalline epinephrine bitartrate and a crystalline solid carrier.

21. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of crystalline epinephrine bitartrate and a crystalline lactose solid carrier.

22. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of micronized crystalline epinephrine bitartrate and a crystalline lactose solid carrier.

23. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of: (i) crystalline epinephrine bitartrate; and (ii) a crystalline lactose solid carrier present at between about 50% w/w to about 99% w/w of the entire formulation.

24. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of crystalline epinephrine bitartrate and a crystalline lactose solid carrier selected from the group consisting of crystalline alpha-lactose monohydrate and a crystalline anhydrous lactose.

25. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of micronized crystalline epinephrine bitartrate and a crystalline lactose solid carrier selected from the group consisting of crystalline alpha-lactose monohydrate and a crystalline anhydrous lactose.

26. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of crystalline epinephrine bitartrate and a crystalline lactose solid carrier selected from the group consisting of crystalline alpha-lactose monohydrate and a crystalline anhydrous lactose, the crystalline lactose solid carrier present at between about 50% w/w to about 99% w/w of the entire formulation, optionally between about 75% w/w to about 99% w/w of the entire formulation.

27. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation consists of or consists essentially of micronized crystalline epinephrine bitartrate and a crystalline lactose solid carrier selected from the group consisting of crystalline alpha-lactose monohydrate and a crystalline anhydrous lactose, the crystalline lactose solid carrier present at between about 50% w/w to about 99% w/w of the entire formulation, optionally between about 75% w/w to about 99% w/w of the entire formulation.

28. The inhalable formulation of any one of the preceding items, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative, such as epinephrine bitartrate, has a Dv50 of between about 1.5 μm to about 3 μm and a Dv90 of between about 2 μm to about 5 μm.

29. The inhalable formulation of any one of the preceding items, wherein the pharmaceutically acceptable salt of epinephrine or epinephrine derivative, such as epinephrine bitartrate, has a fine particle fraction, expressed as a percentage of the fine particle dose relative to the emitted dose, of greater than 30%.

30. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation is substantially unchanged after storage for 6 months or 12 months or 18 months at 25 °C and 60 % relative humidity, optionally wherein "substantially unchanged" means at least 90%, 91%, 92%, 93%, 94% or 95% purity by assay is maintained at these time points.

31. The inhalable formulation of any one of the preceding items, consisting of:

(i) micronized crystalline epinephrine bitartrate having a Dv50 of between about 1.5 μm to about 3 μm and a Dv90 of between about 2 μm to about 5 μm; and

(ii) crystalline α-lactose monohydrate or crystalline anhydrous lactose present at between about 75% w/w to about 99% w/w of the entire formulation,

wherein the inhalable formulation: (a) provides for a fine particle fraction, expressed as a percentage of the fine particle dose relative to the emitted dose, of greater than 30% upon manufacture; and/or (b) is stable for storage for 6 months at 25 °C and 60 % relative humidity.

32. The inhalable formulation of any one of the preceding items, wherein the mass mean aerodynamic diameter (MMAD) is less than 5 microns after storage for 6 months or 12 months or 18 months at 25 °C and 60 % relative humidity.

33. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation provides for a fine particle fraction, expressed as a percentage of the fine particle dose relative to the emitted dose, of greater than 30%, or greater than 35%, or greater than 40% after storage for 6 months or 12 months or 18 months at 25 °C and 60 % relative humidity.

34. The inhalable formulation of any one of the preceding items, wherein the inhalable formulation is a dry powder inhalable formulation.

35. A dry powder inhaler comprising the inhalable formulation of any one of the preceding items.

36. A process of forming the inhalable formulation of any one of item 1 to item 34, including the steps of:

(a) micronizing the pharmaceutically acceptable salt of epinephrine or epinephrine derivative, and

(b) combining the micronized pharmaceutically acceptable salt of epinephrine or epinephrine derivative, with the solid carrier.

37. An inhalable formulation of any one of item 1 to item 34, when produced by the process of item 36.

38. A method of delivering a pharmaceutically acceptable salt of epinephrine or epinephrine derivative, to a subject in need thereof, including the step of:

administering the inhalable formulation of any one of item 1 to item 34 to the subject,

to thereby deliver the pharmaceutically acceptable salt of epinephrine or epinephrine derivative to the subject.

39. A method of treating a disease, disorder or condition responsive to epinephrine in a subject in need thereof, including the step of:

administering the inhalable formulation of any one of item 1 to item 34 to the subject;

to thereby treat the disease, disorder or condition in the subject.

40. The method of item 39, wherein the disease, disorder or condition responsive to epinephrine is selected from the group consisting of anaphylaxis, cardiac arrest, glaucoma, asthma, bronchospasm, croup, and respiratory distress.

41. The method of item 39 or item 40, wherein the method of administering includes the steps of:

providing the inhalable formulation of any one of item 1 to item 34 to the subject; and

allowing the subject to inhale the inhalable formulation,

to thereby treat the disease, disorder or condition in the subject.

42. The method of any one of item 39 to item 41, wherein the step of providing the inhalable formulation includes providing the dry powder inhaler of item 35 to the subject.

43. The method of any one of item 39 to item 42, wherein the method further includes the steps of: (i) monitoring the patient; and (ii) optionally administering further amounts of the inhalable formulation of any one of item 1 to item 34.

Experimental

Example 1: Composition of inhalable epinephrine formulations with lactose monohydrate as carrier

[150] Table 1 shows six epinephrine formulations that were each blended using a Turbula mixer (low shear type mixer). Each formulation contains crystalline micronized epinephrine bitartrate and alpha-lactose monohydrate (Respitose SV003).

Table 1: Epinephrine Blend Compositions.

Blend Code	Epinephrine (%w/w)	Material	Mass (g)
1A	1.2%	Epinephrine Bitartrate	2.183
		alpha-lactose monohydrate (Respitose SV003)	97.817
1B	1.2%	Epinephrine Bitartrate	2.185
		alpha-lactose monohydrate (Respitose SV003)	97.815
1C	4%	Epinephrine Bitartrate	7.277
		alpha-lactose monohydrate (Respitose SV003)	92.723
1D	6%	Epinephrine Bitartrate	10.927
		alpha-lactose monohydrate (Respitose SV003)	89.073
1E	12%	Epinephrine Bitartrate	21.831

		alpha-lactose monohydrate (Respitose SV003)	78.169
1F	12%	Epinephrine Bitartrate	21.853
		alpha-lactose monohydrate (Respitose SV003)	78.147

[151] Blends 1A, 1B, 1C, 1D, and 1E were filled into size 3 HPMC capsules containing 25 mg of blend each. The 1.2%, 4%, 6% and 12% blends correspond to capsule strengths of 0.3 mg, 1.0 mg, 1.5 mg and 3.0 mg epinephrine, respectively.

Example 2: Composition of inhalable epinephrine formulations with mannitol as carrier

[152] Tables 2 and 3 show theoretical and actual inhalable formulations of crystalline epinephrine bitartrate with mannitol as a carrier.

Table 2: Theoretical inhalable epinephrine compositions with mannitol as carrier.

Epinephrine (%w/w)	**Material**	**Theoretical Amount (g)**
1.2%	Epinephrine Bitartrate	2.183
	Mannitol	97.817
4%	Epinephrine Bitartrate	7.277
	Mannitol	92.723
12%	Epinephrine Bitartrate	21.831
	Mannitol	78.169

Table 3: Actual inhalable epinephrine composition with mannitol as carrier.

Blend Code	Epinephrine (%w/w)	Material	Actual Amount (g)
2A	12%	Epinephrine Bitartrate	2.85*
		Mannitol	10.15

*The target drug substance mass of 2.838 g was adjusted to 2.85 g to account for epinephrine potency of the specific lot of epinephrine bitartrate drug substance used in the experiment.

[153] Upon achieving acceptable blending, the formulations were further processed by filling in to glass vials for stability testing. No issues were encountered in performing the powder handling transfers from bulk blend to filled vials.

Example 3: Compositions of inhalable epinephrine formulations with trehalose as carrier

[154] Table 4 and 5 show examples of the theoretical and actual inhalable epinephrine compositions with trehalose as carrier.

Table 4: Theoretical inhalable epinephrine compositions with trehalose as carrier.

Epinephrine (%w/w)	Material	Theoretical Amount (g)
1.2%	Epinephrine Bitartrate	2.183
	Trehalose	97.817
4%	Epinephrine Bitartrate	7.277
	Trehalose	92.723
12%	Epinephrine Bitartrate	21.831
	Trehalose	78.169

Table 5: Actual inhalable epinephrine composition with trehalose as carrier.

Blend Code	Epinephrine (%w/w)	Material	Actual Amount (g)
3A	12%	Epinephrine Bitartrate	2.85*
		Trehalose	10.15

*The target drug substance mass of 2.838 g was adjusted to 2.85 g to account for epinephrine potency of the specific lot of epinephrine bitartrate drug substance used in the experiment.

[155] Upon achieving acceptable blending, the formulations were further processed by filling into glass vials for stability testing. No issues were encountered in performing the powder handling transfers from bulk blend to filled vials.

Example 4: Manufacturing process

Step 1: Micronizing of API (epinephrine bitartrate)

[156] Epinephrine bitartrate drug substance (API) was procured from Transo-Pharm Handels-GmbH (Siek, Germany). Micronization of epinephrine bitartrate (API) was performed using an air jet micronizer (MC Jetmill type 50) and a dosing feeder (K-Tron T20) to deliver the epinephrine bitartrate to the feed chute at a controlled flow rate.

[157] The API was micronized using the following milling process parameters and scale, and achieved the listed yields as shown in table 6:

Table 6: Micronization process parameters, scale and output yield.

Batch Number	Feed Rate (g/min)	Pressure (bar)	Temperature (°C)	Scale (g)	Yield (g)	Yield (%)
E80-18002M1	10.0	12.0	-30	50.00	37.00	78.00
E80-18002M2	10.0	12.0	RT	47.00	39.70	86.60
160916M2	10.0	10.5	RT	295.2	264.6	91.33

[158] Cryogenic micronization using a temperature controlled variable feed system delivering a liquid nitrogen co-feed to the jet mill was used to micronize API in batch

E80-18002M1 and provided for a similarly useful milling process and subsequent formulated inhalable epinephrine blend. Cryogenic micronization was found to be a suitable alternative processing mode of operating the jet mill. Nevertheless, the ambient room temperature (RT) conventional jet milling configuration, without the cryogenic feed system, was also found to be a suitable process for producing inhalable crystalline micronized epinephrine bitartrate and a simpler process configuration. The powders from either processing configuration yielded materials that exhibited distinct X-ray powder diffraction peaks characteristic of epinephrine bitartrate and without substantial evidence of amorphization (loss of crystallinity). Therefore, the micronization process is surprisingly versatile being able to deliver a crystalline powder post milling, whether or not the temperature during milling is uncontrolled ambient, or whether it is controlled to cryogenic low temperature conditions. Since some API materials undergo a substantial extent of amorphization during air jet milling (micronization), cryogenic milling is sometimes an essential more complex processing configuration to produce an inhalable drug substance powder without loss of crystallinity. Epinephrine bitartrate was surprisingly found to not necessarily require this, giving a simpler process option with versatility to operate at ambient or colder temperatures where desired.

[159] The powders pre and post micronization were analyzed for particle size using a laser diffraction system in dry powder sample preparation mode (Sympatec Helos, Clausthal-Zellerfeld, Germany). From the particle size analyses, the data for volume based mean particle size (Dv50), the cumulative 90% of volume size (Dv90), and the total volume of particles with size below 5 µm values are summarised in Table 7.

Table 7: Micronization results.

Customer Batch Number	**Sample**	**Dv50 (µm)**	**Dv90 (µm)**	**Volume below 5 µm (%)**
E80-18002	Unmicronised	37.50	193.89	8.18
E80-18002M1	Trial 1	1.62	3.23	99.52
	Drum 1	1.65	3.55	98.39
E80-18002M2	Trial 1	1.57	3.38	98.91

	Drum 1	1.52	3.25	99.20
160916M2	Trial 1	1.83	3.76	97.77
	Drum 1 bottom	1.77	3.65	98.37
	Drum 1 top	1.83	3.71	98.27
	Final Sample	1.79	3.65	98.42

[160] Crystalline epinephrine bitartrate was found to micronize in a robust manner in scales ranging from 50g to 300g. For powders to impact and deposit in the deep lung, it is generally accepted that the portion of particles in the 0.5 – 5 μm size range are particularly suitable for this. Larger diameter particles may impact the throat or upper airways, and finer particles may to some extent be exhaled. Therefore, the particle size analysis data indicates that micronization via conventional ambient (RT) or cryogenic milling conditions is useful to convert the procured epinephrine bitartrate from an essentially non-deliverable state via the lung, into a bulk drug substance of epinephrine bitartrate that is essentially less than 5 μm and where the mean size is within the desired 0.5 – 5 μm size range. Therefore, micronization is useful for processing epinephrine for inhaled drug delivery, without loss of crystallinity.

Step 2: Low shear mixing of epinephrine bitartrate and lactose monohydrate

[161] Prior to blending, the micronized epinephrine bitartrate was passed through a 250 μm mesh sieve to eliminate any level of agglomeration, if present.

[162] The first blending step involved mixing the epinephrine bitartrate with an equivalent amount of lactose monohydrate and this mixture was blended in a Turbula mixer at approximately 34 rpm for approximately 30 mins.

[163] The remainder of the lactose monohydrate required for the formulation was split into three equivalent amounts.

[164] Three additional blending steps were performed by mixing one third of the remaining lactose monohydrate into the powder bulk, followed by blending in a Turbula mixer at approximately 34 rpm for approximately 30 mins.

[165] After resting, the final formulation was passed through a 250 μm mesh sieve twice before being returned to the blending vessel. The formulation was manually rotated before sampling.

[166] Blend uniformity testing results of the 1.2% (Blend Code 1B) and 6% (Blend Code 1D) formulations are summarised in Table 8.

Table 8: Crystalline micronized blended epinephrine blend uniformity testing results, tested by representative sampling and HPLC analysis (n=10).

Blend Code	**Epinephrine (% w/w)**	**Assay Mean (% w/w)**	**Uniformity of the Blend %Relative Standard Deviation (%RSD)**
1B	1.2	1.2	2.3
1D	6	6.2	1.6

[167] The formulation blend exhibited a high degree of blend uniformity and expected assay (potency). The bulk powder was further processed via accurate weight-based filling into capsules and packaged into sealed glass jars without a desiccant. Sample capsules from each lot containing 25 mg of blend were loaded into a Plastiape RS01 dry powder inhaler device with a shortened mouthpiece and tested using a Next Generation Impactor (NGI). The aerosol was characterized for aerodynamic particle size distribution (APSD), summarised in Table 9.

Table 9: Aerodynamic particle size data of crystalline micronized lactose blended epinephrine bitartrate (NGI results).

Blend Code	**Epinephrine (mg) per 25mg Capsule**	**Epinephrine (% w/w)**	**MMAD (μm)**	**FPF[a] (%)**	**FPD <5μm (mg)**
1B	0.3	1.2	2.4	45.25	0.11
1D	1.5	6	3.1	40.67	0.43

[a]Fine Particle Fraction (FPF) expressed as a percentage of the fine particle dose relative to the emitted dose.

[168] This APSD data indicates the blend performed surprisingly well in the RS01 device. The mass mean aerodynamic diameter (MMAD) was found to be well within the desired 0.5-5 μm range. The fine particle fraction (FPF) was observed to be significantly higher than the typical range of approximately 25 – 30% often observed for DPI devices, which suggests the crystalline micronized epinephrine bitartrate particles were efficiently deagglomerated from the carrier lactose particles during the aerosolization. Therefore, useful fine particle doses (FPD) were observed indicating a substantial quantity of the capsule drug content would be delivered to the deep lung of a patient in need of epinephrine. For reference intramuscular administration of epinephrine via autoinjector to an adult anaphylaxis patient is prescribed at 0.3 mg per injection. Therefore, the blends prepared in this example achieved inhalation delivery fine particle doses (FPD) by NGI testing that bracket this useful therapeutic drug dose level (0.11 – 0.43 mg epinephrine).

[169] A 6 month timepoint study was performed on an epinephrine bitartrate and lactose monohydrate formulation (Blend Code 8B) with an epinephrine potency of 12% w/w. The results of Next Generation Impactor testing at each time point after being held at 25 °C/60% RH are summarised in Table 10.

Table 10: Next Generation Impactor results for 12% w/w epinephrine blend (Blend Code 8B).

Timepoint	**MMAD (μm)**	**FPD < 5μm (mg)**	**FPF (%)**
Initial	3.6	0.62	25.98
1 month	3.7	0.55	22.67
3 month	3.7	0.51	21.31
6 month	4.4	0.42	17.71

[170] Results of Next Generation Impactor testing over 6 months storage show consistent key parameters for inhalation delivery including the desired MMAD range and FPD levels higher than the expected minimum necessary for treating a patient in need via inhalation, and without use of an intramuscular injection.

OR Step 2: High shear mixing of epinephrine bitartrate and lactose monohydrate

[171] Epinephrine bitartrate was passed through a 250 μm mesh sieve to eliminate any level of agglomeration, if present.

[172] A quantity of epinephrine bitartrate equivalent to 5.2% w/w epinephrine was added to a Diosna P1-6 (Germany) high shear mixer bowl with alpha-lactose monohydrate, layering the active ingredient between equal portions of the lactose.

[173] The manufacturing and sampling parameters listed in Table 11 were used in a successive manner for blending the remaining blend from the respective previous run.

Table 11: Manufacturing and sampling parameters for high shear blending of crystalline epinephrine bitartrate with alpha-lactose monohydrate.

Run Number	Impeller Speed (RPM)	Granulator Speed (RPM)	Time for Sampling
1	150	0	2 minutes 15 minutes 30 minutes
2	300	0	15 minutes 30 minutes
3	600	0	15 minutes 30 minutes

[174] Following mixing, powder samples were taken representatively from various locations in the mixing bowl and tested by HPLC for blend uniformity. Additional blend uniformity testing was performed following a 4 day and 7 day resting period. The uniformity results are summarised in Table 12.

Table 12: Epinephrine blend uniformity testing results following high shear mixing

Resting Period	Run	Blending Time (mins)	Assay Mean (% w/w)	%RSD
Day 0	1	2	5.2	3.9
		15	5.2	5.2
		30	5.1	15.9
	2	15	5.0	11.9
		30	5.1	8.8
		30	5.2	6.3
	3	15	5.2	6.4
		30	5.1	4.7
Day 4	1	30	5.1	4.6

	2	30	5.3	7.0
	3	30	5.3	3.4
Day 7	1	30	5.1	2.7
	2	30	5.2	4.4
	3	30	5.1	3.2

[175] The formulation blends for Run 1 and Run 3 were further processed by accurately filling into capsules at 25 mg fill mass target, then loaded into a Plastiape RS01 dry powder inhaler device with a shortened mouthpiece and tested using a Next Generation Impactor. The results are summarised in Table 13.

Table 13: Next Generation Impactor results.

Run	**MMAD (µm)**	**FPD < 5µm (mg)**	**FPF[a] (%)**
1	2.65	0.38	41.84
3	2.66	0.39	44.77

[a]Fine Particle Fraction (FPF) expressed as a percentage of the fine particle dose relative to the emitted dose.

[176] Results of Next Generation Impactor testing of impeller speeds from 150RPM to 600RPM show consistent key parameters for inhalation delivery with MMAD in the desired 1-5 µm range for delivery to the deep lung, and with fine particle dose very close to and slightly higher than the 0.3 mg prescribed dose for autoinjector intramuscular delivery of epinephrine to a patient suffering anaphylaxis and in need of epinephrine.

[177] This data also demonstrates that crystalline micronized epinephrine bitartrate formulated with lactose can be efficiently mixed by either low shear or high shear blending methods (for example the use of Turbula and Diosna equipment here, or other similar mixing machine brands and types). In some cases a high shear mixing process may be more readily scaled up to a larger batch size, and in other cases, small scale lots are more convenient to blend via low shear methods. The data surprisingly shows that crystalline micronized epinephrine bitartrate can be blended in a robust processing manner regardless of the type of mixing equipment's (level of shear force). Further the APSD data verifies that useful MMAD and FPD performance characteristics were observed regardless of the type of mixing technology applied.

Example 5: Agglomeration experiments with epinephrine bitartrate and Magnesium Stearate

[178] Particle size distribution was analysed at different time points on the micronized epinephrine bitartrate alone. The results comparing the initial testing time point to the 4 week time point are summarised in Table 14.

Table 14: Particle size distribution of micronized epinephrine bitartrate.

Time Point	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	Volume below 10 µm (%)
Initial	0.310	1.73	57.8	79.94
4 weeks (2-8°C)	3.49	248	847	22.62
4 weeks (40°C/75%RH)	2.40	294	1200	30.53

[179] Figures 1 to 3 show scanning electron microscope images corresponding to the three time points in Table 14.

[180] Based on the profound increase in all particle size parameters and the decrease in the proportion of the particles below 10 µm, it is obvious that the crystalline micronized epinephrine bitartrate alone, without the addition of lactose monohydrate as a carrier, naturally tends to agglomerate. This extent of agglomeration is overly high for a DPI product since the proportion of the drug available to be delivered to the deep lung would be substantially reduced potentially to sub-therapeutic dosing levels due to the agglomeration.

[181] The particle size distribution was analysed at different time points on the crystalline micronized epinephrine bitartrate with the addition of magnesium stearate (MgSt). The results comparing the initial testing time point to the 4 week timepoint are summarised in Table 15.

Table 15: Particle size distribution of micronized epinephrine bitartrate and MgSt.

Time Point	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	Volume below 10 µm (%)
Initial	0.265	1.15	4.2	94.88

4 weeks (2-8°C)	0.952	95.1	524	33.78
4 weeks (40°C/75%RH)	8.07	181	434	10.82

[182] Figures 4 to 6 show scanning electron microscope images corresponding to the three time points in Table 15.

[183] Magnesium stearate is commonly used as a lubricant excipient or force control agent in DPI formulations to assist in breaking up inter-particle and particle/surface attractive forces allowing a better dispersion of fine drug particles. It is clear from the results in table 15 that the formulation with magnesium stearate still tends to agglomerate even though it might be expected in the art that magnesium stearate would be a useful functional excipient for avoiding or minimizing agglomeration.

Example 6: Agglomeration Experiments with the addition of lactose monohydrate

[184] Table 16: Crystalline micronized epinephrine bitartrate formulation with alpha-lactose monohydrate as carrier.

Formulation	**Drug Amount (g)**	**Carrier**	**Magnesium Stearate Content (g)**	**Scale (g)**
1	0.2	Lactose Monohydrate	-	2
2	0.2	Lactose Monohydrate	0.04	2

[185] The formulations were manufactured with alpha-lactose monohydrate in a 10%w/w API loading with micronized crystalline epinephrine bitartrate material. Prior to blending, the API was passed through a 250 μm sieve using a pallet knife with moderate manual force to assist the powder passing the screen. No large particles remained on the sieve mesh post-sieving. The blends were then produced by layering the API with the excipient carrier and magnesium stearate, where appropriate, in a glass vial and mixing by Turbula for approximately 30 min at approximately 34 rpm.

[186] Figures 7 (A. Epinephrine formulation, pre-blending; B. Epinephrine formulation, post-blending) and 8 (A. Epinephrine formulation, pre-blending, + MgSt; B. Epinephrine formulation, post-blending, + MgSt) show that both formulations of table 16 pre- and immediately post-mixing are free from loose agglomerates.

Example 7a: High chemical and physical stability of formulation

[187] A 6 month duration stability study was performed on an epinephrine bitartrate and lactose monohydrate formulation (Blend Code 8B) with an epinephrine blend potency of 12% w/w. The results of stability testing at each time point after being held at 25°C/60%RH are summarised in Table 17a. Note at 25 mg per capsule blend fill weight target, this corresponds to 3.0 mg epinephrine strength per capsule.

[188] Blend 1E was tested for stability up to 18 months at 25°C/60%RH and the results are described in Table 17b.

Table 17a: Summary of 6 months chemical and physical stability data of an epinephrine bitartrate and lactose monohydrate formulation (Blend Code 8B) stored at 25°C/60%RH.

Test		Initial		1 month		3 month		6 month	
Assay (n=2) mg/capsule		3.0		3.1		3.2		3.0	
Related Substances (n=2) (%impurity)		RT	%	RT	%	RT	%	RT	%
	Imp A	3.16	0.12	3.28	0.13	3.18	0.12	3.29	0.06
	Imp B					0.85	0.06	0.85	<0.05
	Imp D					3.32	<0.05		
Mean FPD (mg) (≤ 5 µm) (n=3)		0.62		0.55		0.51		0.42	
Mean FPF (FPD as % total dose) ≤ 5 µm (n=3)		25.98		22.67		21.31		17.71	
Mean MMAD (µm) (n=3)		3.6		3.7		3.7		4.4	
Mean GSD (n=3)		1.7		1.7		1.7		1.8	
Mean Total Delivered Dose (n=10) (mg)		30L/min	2.00	30L/min	2.17	30L/min	2.11	30L/min	2.08
		60L/min	2.26	60L/min	2.23	60L/min	2.33	60L/min	2.21
		90L/min	2.22	90L/min	2.01	90L/min	2.28	90L/min	2.37

Water content (n=3) (%)	4.15	4.10	4.04	3.98

RT – retention time on the HPLC chromatograph used for analysis of impurities, FPD – Fine Particle Dose, FPF – Fine Particle Fraction, MMAD – Mass Median Aerodynamic Diameter, GSD – Geometric Standard Deviation; Related Substances impurities have a limit of quantification of 0.05%; Testing was performed with a Plastiape RS01 that was modified to have a shorter mouthpiece.

Table 17b: Summary of 18 months chemical and physical stability data of an epinephrine bitartrate and lactose monohydrate formulation (Blend Code 1E / Batch BN022/21 3.0 mg strength) stored at 25°C/60%RH.

Test	3 Month	6 Month	12 Month	18 Month
Assay (%LC, HPLC)	100	98	99	97
Mean metered dose (10 capsules) (% LC)	91	98	97	99
Mass median aerodynamic diameter by NGI (µm) (mean of 3 capsules)	3	3	3	3
Fine particle dose by NGI (Mean of 3 capsules)	0.97	1.00	1.00	0.98
Fine particle fraction by NGI (mean of 3 capsules)	46	50	48	47
Each specified impurity (%, HPLC)	< 0.3	<0.3	<0.3	<0.3
Impurity A	< 0.2	<2.5	<2.5	<2.5
Impurity B	< 0.2	<0.2	<0.2	<0.2
Impurity C	< 0.1	<0.1	<0.1	<0.1
Impurity D	< 0.1	<0.1	<0.1	<0.1
Impurity E	< 2	<3.5	<3.5	<3.5
Total impurities (%, HPLC)				
Water content (n=3) (%)	4.2	4.3	4.2	

[189] Example 7a demonstrated that a representative blend of epinephrine bitartrate blended with alpha-lactose monohydrate exhibited high chemical stability over 6 and 18 months storage and testing at 25°C and 60% relative humidity, which is the storage condition used to simulate controlled room temperature stored pharmaceutical products. There was no significant change in assay from the 3.0mg/capsule initial state. The impurity profile assessed by HPLC analysis with a limit of quantitation of 0.05% indicated that no impurities grew significantly over even 18 months of storage, with impurity A remaining at a similar level over the 18 months, without any significant

growth over time on storage. Impurity B was detected at about the limit of quantitation at 3 months and again numerically at 0.03% at the 6 month time point, but at that trace level, the quantity was less than the limit of quantitation. The water content did not exhibit significant change over the 6 months period, and the majority of the water mass quantified corresponds to the weight of the monohydrate water in the lactose excipient. This suggests there was no significant moisture uptake or loss in the blend over the 6 month storage period. Similar observations can be made from Table 17b even over an extended 18 month period of testing. Therefore, the encapsulated blend of crystalline micronized epinephrine bitartrate with alpha-lactose monohydrate exhibited highly stable chemical properties over 18 months of stability storage and supportive of a convenient room temperature stored pharmaceutical product. Further, Example 7a demonstrated that a representative blend of epinephrine bitartrate blended with alpha-lactose monohydrate exhibited high physical stability over the 18 month period of storage and testing at 25°C and 60% room humidity, which is the storage condition used to simulate controlled room temperature stored pharmaceutical products.

[190] The aerosol performance properties tested indicated appropriate mean total delivered dose of epinephrine across a wide range of inspiratory flow rates (tested by Next Generation Impactor, NGI and with an RS01 Plastiape DPI high resistance modified device). The mass mean aerodynamic diameter (MMAD) remained significantly below the 5 micron threshold and with consistently low variability (GSD) supporting delivery to the deep lung of crystalline micronized epinephrine bitartrate from the lactose blend throughout the storage testing period. Figure 9 is a graphical representation of the NGI testing for Batch BN021/21 1.0mg strength capsules which had been stored at 25°C/60% RH for 18 months. The graph shows the optimal distribution of epinephrine across stages 3 to 5 representing delivery to the deep lung. Therefore, the encapsulated blend of crystalline micronized epinephrine bitartrate with alpha-lactose monohydrate exhibited highly stable physical properties over an unexpected 18 months of stability storage and supportive of a convenient room temperature stored dry powder inhalation delivered pharmaceutical product.

Example 7b: High chemical and physical stability of formulation

[191] Similarly to Example 7a, Blend Code 1C was processed and then accurately filled into Size 3 HPMC capsules in an equivalent manner to Example 4 Step 2. The capsules were packaged into HDPE bottles with desiccant and stored for 6 months at 25°C/60%RH and 40°C/75%RH.

[192] The results of stability testing at each time point after being held at 25°C/60%RH are summarised in Table 18. Note at 25 mg per capsule blend fill weight target, this corresponds to 1.0 mg epinephrine strength per capsule.

Table 18: Summary of 18 months chemical and physical stability data of an epinephrine bitartrate and lactose monohydrate formulation (Blend Code 1C) stored at 25°C/60%RH.

Test	Initial	1 month	3 month	6 month	18 month
Assay (n=2) (%)	95	96	98	97	96
Related Substances (n=2) Impurity B (%)	<0.2	<0.2	0.20	<0.2	0.2
Mean FPD (mg) (≤ 5 µm) (n=3)	0.28	0.28	0.28	0.32	0.35
Mean FPF (FPD as %) ≤ 5 µm (n=3)	44	46	44	52	50
Mean MMAD (µm) (n=3)	2	2	2	2	2
Mean Metered Dose (n=10) (% LC)	92	94	95	95	95
Water content (n=3) (%)	4.8	4.9	4.8	4.9	4.8

FPD – Fine Particle Dose, FPF – Fine Particle Fraction expressed as a percentage of the fine particle dose relative to the emitted dose, MMAD – Mass Median Aerodynamic Diameter, Related Substances impurities have a limit of quantification of 0.05%, the following Related Substances were within the specified acceptance criteria: Impurity A – <0.3, Impurity C – <0.2, Impurity D – <0.1, Impurity E – <0.1, Each Unspecified Impurity – <0.5; Impurity B was the only impurity that was detected and quantified across the testing time points; Testing was performed with a Plastiape RS01 that was modified to have a shorter mouthpiece.

[193] The results of stability testing at each time point after being held at 40°C/75%RH are summarised in Table 19. Note at 25 mg per capsule blend fill weight target, this corresponds to 1.0 mg epinephrine strength per capsule.

Table 19: Summary of 6 months chemical and physical stability data of an epinephrine bitartrate and lactose monohydrate formulation (Blend Code 1C) stored at 40°C/75%RH.

Test	Initial	1 month	3 month	6 month
Assay (n=2) (%)	95	96	99	97
Related Substances (n=2) Impurity B (%)	<0.2	<0.2	<0.2	0.31
Mean FPD (mg) (≤ 5 µm) (n=3)	0.28	0.34	0.29	0.34
Mean FPF (FPD as %) ≤ 5 µm (n=3)	44	48	45	49
Mean MMAD (µm) (n=3)	2	2	2	2
Mean Metered Dose (n=10) (% LC)	92	94	96	95
Water content (n=3) (%)	4.8	4.9	4.9	4.8

FPD – Fine Particle Dose, FPF – Fine Particle Fraction expressed as a percentage of the fine particle dose relative to the emitted dose, MMAD – Mass Median Aerodynamic Diameter, Related Substances impurities have a limit of quantification of 0.05%, the following Related Substances were within the specified acceptance criteria: Impurity A – <0.3, Impurity C – <0.2, Impurity D – <0.1, Impurity E – <0.1, Each Unspecified Impurity – <0.5; Impurity B was the only impurity that was detected and quantified across the testing time points; Testing was performed with a Plastiape RS01 that was modified to have a shorter mouthpiece.

[194] Example 7b demonstrates similarly useful stability results for a 1.0 mg strength capsule. Further packaging in HDPE bottles with desiccant corresponded to superior stability properties at real time and accelerated storage conditions.

Example 8: Addition of lactose fines

[195] During the 6 month stability study in Example 7, additional formulations were blended to assess how the inclusion of fine alpha-lactose monohydrate carrier particles would affect the stability and performance of the formulation stored at 25°C/60%RH.

[196] Respitose SV003 was used as the coarse lactose carrier, and Lactohale LH300 was used as the fine lactose carrier particles. Both fine and coarse lactose materials were alpha-lactose monohydrate. Different ratios of lactose fines were mixed with either the standard crystalline micronized epinephrine bitartrate or cryogenically micronized epinephrine bitartrate as summarised in Table 20.

Table 20: Formulations with coarse lactose and lactose fines.

Blend Code	**Formulation**	**API**	**API*(% w/w)**	**Coarse Carrier (%w/w)**	**Fine Carrier (%w/w)**
8A	A	E80-18002M1 (Cryo milled)	22.4	77.6	0
8B	B	E80-18002M2 (Standard Milled)	22.4	77.6	0
8C	C	E80-18002M2 (Standard Milled)	22.4	74.6	3
8D	D	E80-18002M2 (Standard Milled)	22.4	67.6	10
8E	E	E80-18002M1 (Cryo milled)	22.4	74.6	3

*adjusted for purity and salt/base conversion to achieve an epinephrine blend potency of 12% w/w

[197] Assay results were as expected for all formulations and were consistent with the previous time points verifying the product potency was stable across the storage period regardless of the presence of lactose fines or the ratio of fines to coarse lactose materials in the blends.

[198] The MMAD for all formulations plateaued after the one month time point, apart from Formulation B which had increased slightly. For Formulation A the FPD stayed relatively consistent after the 3 month time point, and the %FPF appeared to have stabilised at the 1 month time point. For Formulation B, the FPD and %FPF decreased with each subsequent time point. For Formulation C the FPD at the 6 month time point was consistent with the previous time point. The %FPF increased slightly since the 3 month time point. For Formulation E, the FPD had increased since the 3

month time point, and was higher than the initial time point. The %FPF remained relatively consistent across all time points.

[199] Formulation A showed the highest proportion of deposition with particles in the 0-3μm, with a distribution indicative of deep lung delivery.

[200] The delivered dose results at the 6 month time point for all formulations were consistent with the initial time point. Water content was around 4% for all formulations, which was consistent with the previous time points. The %RSD was low for all formulations.

Example 9: Stability of epinephrine bitartrate + α-lactose monohydrate formulation vs epinephrine bitartrate + α-lactose monohydrate + magnesium stearate formulation

[201] A composition of epinephrine bitartrate + α-lactose monohydrate, only, demonstrated significantly superior chemical stability over an epinephrine bitartrate + α-lactose monohydrate + magnesium stearate formulation as is demonstrated in tables 21 and 22, below. This is surprising since, based on the lack of stability and the significant agglomeration observed with the epinephrine bitartrate alone, it was expected that the addition of magnesium stearate would be required to achieve the necessary stability for storage. The sum of related substances developing over a period of 1 month of stressed storage shows minimum increase for epinephrine bitartrate + α-lactose monohydrate. Meanwhile, for the epinephrine bitartrate + α-lactose monohydrate + magnesium stearate formulation, the related substances increased dramatically with most of this being a degradant product at an approximate RRT of 3.07. This data indicates a surprising level of chemical incompatibility with magnesium stearate. Total impurities increased from 0.19% at T=zero to 2.88% at T=1month in the presence of magnesium stearate, but on 0.17% at T=zero to 0.35% at T=1 month in the lactose blend without magnesium stearate.

[202] Therefore, good chemical compatibility was observed in the absence of magnesium stearate, a common formulating agent, and with the simpler composition of only a lactose monohydrate carrier. By contrast to the typical functional effects of lactose

and magnesium stearate excipients, magnesium stearate was ineffective to prevent agglomeration of epinephrine bitartrate and in fact created difficulties. Meanwhile lactose, a carrier excipient, was surprisingly effective in mitigating the tendency of epinephrine bitartrate to self-agglomerate and enabling a useful inhalable formulation with improved chemical and physical stability compared to those containing magnesium stearate.

Table 21: Results from related substances testing of 10% micronized epinephrine bitartrate + lactose monohydrate.

Relative RT	Initial			1 week			2 week			1 month		
	%Area		Mean	%Area		Mean	%Area		Mean	%Area		Mean
	Rep 1	Rep 2		Rep 1	Rep 2		Rep 1	Rep 2		Rep 1	Rep 2	
0.86	ND	ND	ND	0.05	0.06	0.06	ND	ND	ND	ND	ND	ND
3.07	ND	ND	ND	0.06	0.07	0.07	0.09	0.09	0.09	0.21	0.22	0.22
3.11 (impurity A)	0.17	0.17	0.17	0.17	0.20	0.19	0.20	0.18	0.19	0.13	0.13	0.13
Sum	0.17	0.17	0.17	0.28	0.33	0.31	0.29	0.27	0.28	0.34	0.35	0.35

ND – not detected

Table 22: Results from related substances testing of 10% micronized epinephrine bitartrate + lactose monohydrate + magnesium stearate.

Relative RT	Initial			1 week			2 week			1 month		
	%Area		Mean	%Area		Mean	%Area		Mean	%Area		Mean
	Rep 1	Rep 2		Rep 1	Rep 2		Rep 1	Rep 2		Rep 1	Rep 2	
0.41	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.14	0.14	0.14
0.65	ND	ND	ND	ND	ND	ND	0.06	0.06	0.06	0.08	0.08	0.08
0.86	ND	ND	ND	0.12	0.10	0.11	ND	ND	ND	ND	ND	ND
1.63	ND	ND	ND	ND	ND	ND	0.08	0.08	0.08	0.26	0.26	0.26
1.88/1.89	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.09	0.09	0.09
3.06/3.08	ND	ND	ND	0.53	0.49	0.51	0.81	0.80	0.80	1.39	1.37	1.38
3.10 (impurity A)	0.19	0.19	0.19	0.43	0.39	0.41	0.57	0.54	0.56	0.83	0.82	0.83
3.17/3.18	ND	ND	ND	ND	ND	ND	ND	ND	ND	0.10	0.10	0.10
Sum	0.19	0.19	0.19	1.08	0.98	1.03	1.52	1.48	1.50	2.89	2.86	2.88

ND – not detected

[203] The tables of data clearly indicate a surprising level of chemical stability is achieved with epinephrine bitartrate blended with lactose alone, but not with the further addition of magnesium stearate to the epinephrine/lactose blend. This is surprising

considering magnesium stearate is one of the most widely used excipients in pharmaceutical products and unusual to see this level of chemical incompatibility with magnesium stearate. Further it is surprising that a lubricant (or force control agent), most commonly as magnesium stearate in DPI products, was not required at all to mitigate the strong tendency of micronized crystalline epinephrine bitartrate to self-agglomerate. A simple blending with lactose monohydrate was found to be both chemically more stable than with magnesium stearate also added, and the self-agglomeration tendency of the API was no longer seen once blended simply with lactose monohydrate. It was unexpected and useful that a simpler composition of API with lactose has such a positive influence on chemical and physical stability.

[204] The more complex processing method of spray drying, and which converts the crystalline solid state to essentially an amorphous solid state, is commonly used in DPI products and reported by others for epinephrine. Spray drying requires specialized expensive processing equipment and facilities. It is a processing technology that is less available at contract manufacture sites. It requires use of organic solvents in processing that may leave residuals in the powdered product, and also necessitates specific site licensing and abatement systems to permit processing with such solvents. Furthermore, the process yields of spray drying are generally less than conventional micronization, and the amorphous spray dried products are thermodynamically less stable than crystalline products. For all these reasons, micronization and lactose blending are preferred and simpler processing techniques than spray drying. The simple formulation and processing conceived here of micronization of crystalline epinephrine bitartrate and blending with lactose, filled into a capsule and loaded into a dry powder inhaler was found to deliver a process and product highly useful for pharmaceutical product purposes to deliver epinephrine via a DPI to a patient in need thereof.

CLAIMS:

1. An inhalable formulation, comprising:

(i) a pharmaceutically acceptable salt of epinephrine or a pharmaceutically acceptable salt of an epinephrine derivative; and

(ii) a solid carrier.

2. The inhalable formulation of claim 1, wherein the pharmaceutically acceptable salt of epinephrine or pharmaceutically acceptable salt of an epinephrine derivative is present at between about 0.01 to about 5.0 mg per unit dose of the formulation

3. The inhalable formulation of claim 1 or claim 2, wherein the pharmaceutically acceptable salt of epinephrine or pharmaceutically acceptable salt of an epinephrine derivative, is a salt selected from the group consisting of bitartrate, hydrochloride, maleate, malate, malonate, borate and fumarate, and mixtures thereof.

4. The inhalable formulation of any one of the preceding claims, wherein the epinephrine derivative is selected from the group consisting of norepinephrine, dopamine, 3-methoxytyramine, synephrine, *p*-octopamine and/or salts and mixtures thereof.

5. The inhalable formulation of any one of the preceding claims, wherein the solid carrier is selected from the group consisting of alpha-lactose monohydrate, beta-lactose, an anhydrous lactose, mannitol, sucrose, and trehalose.

6. The inhalable formulation of any one of the preceding claims, wherein the inhalable formulation consists essentially of the pharmaceutically acceptable salt of epinephrine or pharmaceutically acceptable salt of an epinephrine derivative; and a solid carrier.

7. The inhalable formulation of any one of the preceding claims, wherein the inhalable formulation does not comprise any other excipients than the solid carrier.

8. The inhalable formulation of any one of the preceding claims, wherein the inhalable formulation does not comprise a pH buffer agent.

9. The inhalable formulation of any one of the preceding claims, wherein the inhalable formulation consists or consists essentially of epinephrine bitartrate and a solid carrier, preferably crystalline epinephrine bitartrate and a solid carrier.

10. The inhalable formulation of any one of the preceding claims, wherein the inhalable formulation consists or consists essentially of epinephrine bitartrate and a lactose solid carrier, optionally alpha-lactose monohydrate solid carrier.

11. The inhalable formulation of any one of the preceding claims, wherein the solid carrier is present within the inhalable formulation at between about 50% w/w to 99% w/w of the entire formulation.

12. A dry powder inhaler comprising the inhalable formulation of any one of the preceding claims.

13. A process of forming the inhalable formulation of any one of claim 1 to claim 11, including the steps of:

(a) micronizing the pharmaceutically acceptable salt of epinephrine or pharmaceutically acceptable salt of an epinephrine derivative, and

(b) combining the micronized pharmaceutically acceptable salt of epinephrine or pharmaceutically acceptable salt of an epinephrine derivative, with the solid carrier.

14. An inhalable formulation of any one of claim 1 to claim 11, when produced by the process of claim 13.

15. A method of delivering epinephrine to a subject in need thereof, including the step of:

administering the inhalable formulation of any one of claim 1 to claim 11 to the subject,

to thereby deliver the epinephrine to the subject.

16. A method of treating a disease, disorder or condition responsive to epinephrine in a subject in need thereof, including the step of:

administering the inhalable formulation of any one of claim 1 to claim 11 to the subject;

to thereby treat the disease, disorder or condition in the subject.

17. The method of claim 16, wherein the disease, disorder or condition is selected from the group consisting of anaphylaxis, cardiac arrest, glaucoma, asthma, bronchospasm, croup, and respiratory distress.

18. The method of claim 16 or claim 17, wherein the method of administering includes the steps of:

providing the inhalable formulation of any one of claim 1 to claim 11 to the subject; and

allowing the subject to inhale the inhalable formulation,

to thereby treat the disease or condition in the subject.

19. The method of any one of claim 16 to claim 18, wherein the step of providing the inhalable formulation includes providing the dry powder inhaler of claim 12 to the subject.

20. The method of any one of claim 16 to claim 19, wherein the method further includes the steps of: (i) monitoring the patient; and (ii) optionally administering further amounts of the inhalable formulation of any one of claim 1 to claim 11.

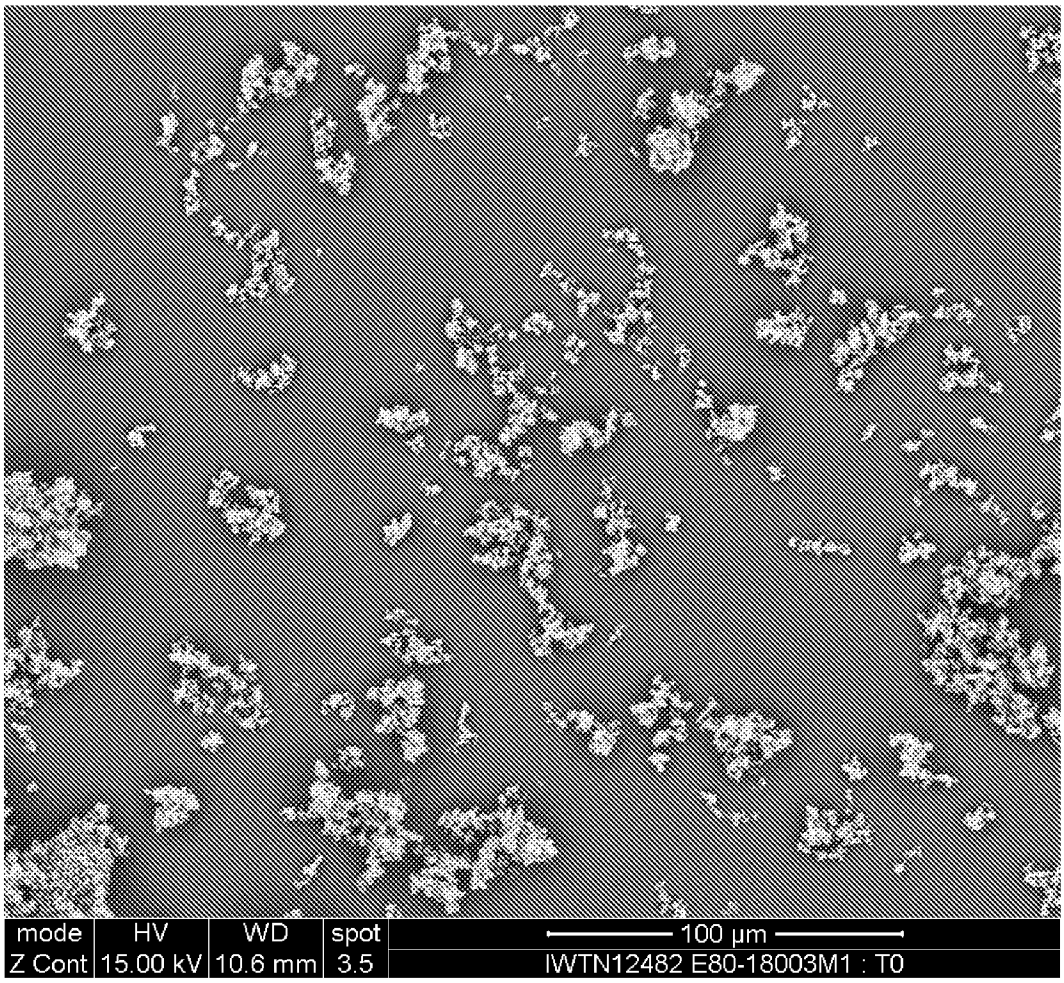

mode
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Z Cont
15.00 kV
10.6 mm
3.5
IWTN12482 E80-18003M1 : T0

FIGURE 1

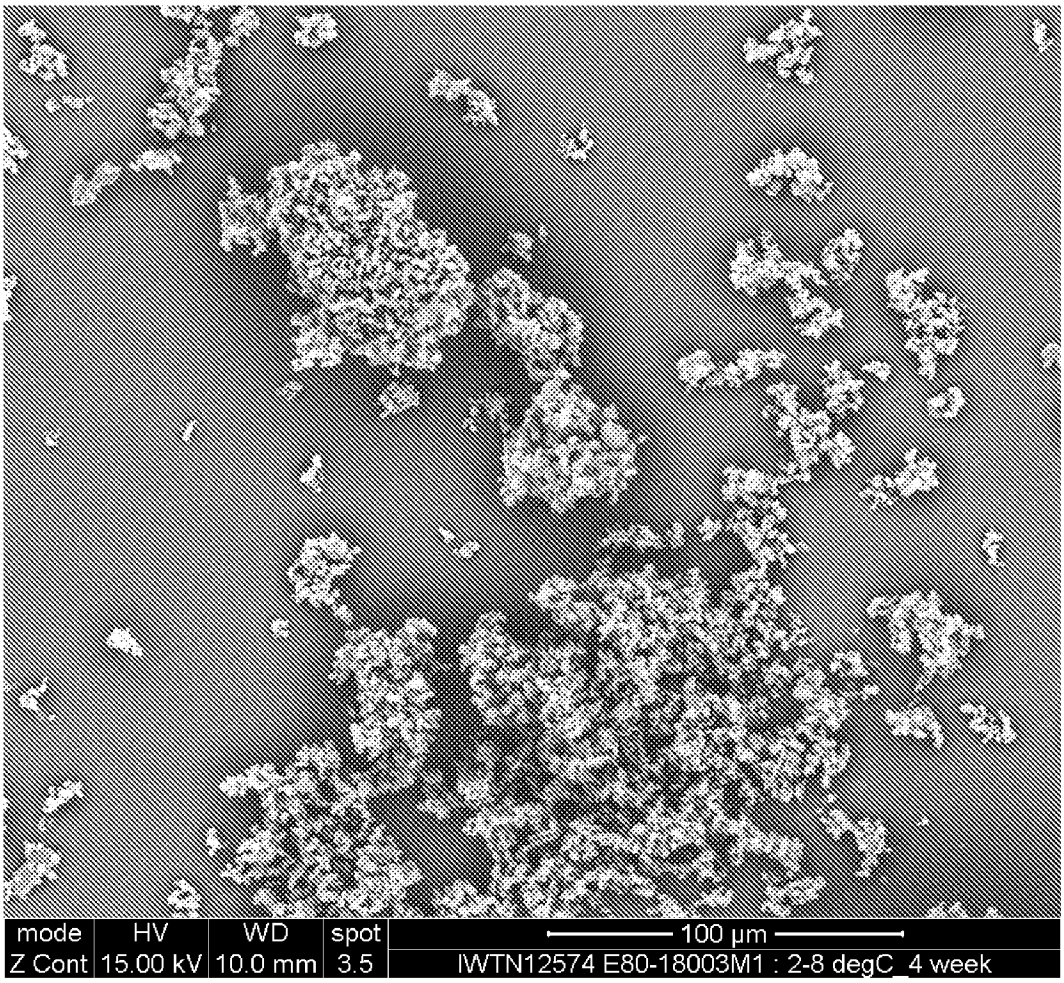

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Z Cont
15.00 kV
10.0 mm
3.5
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FIGURE 2

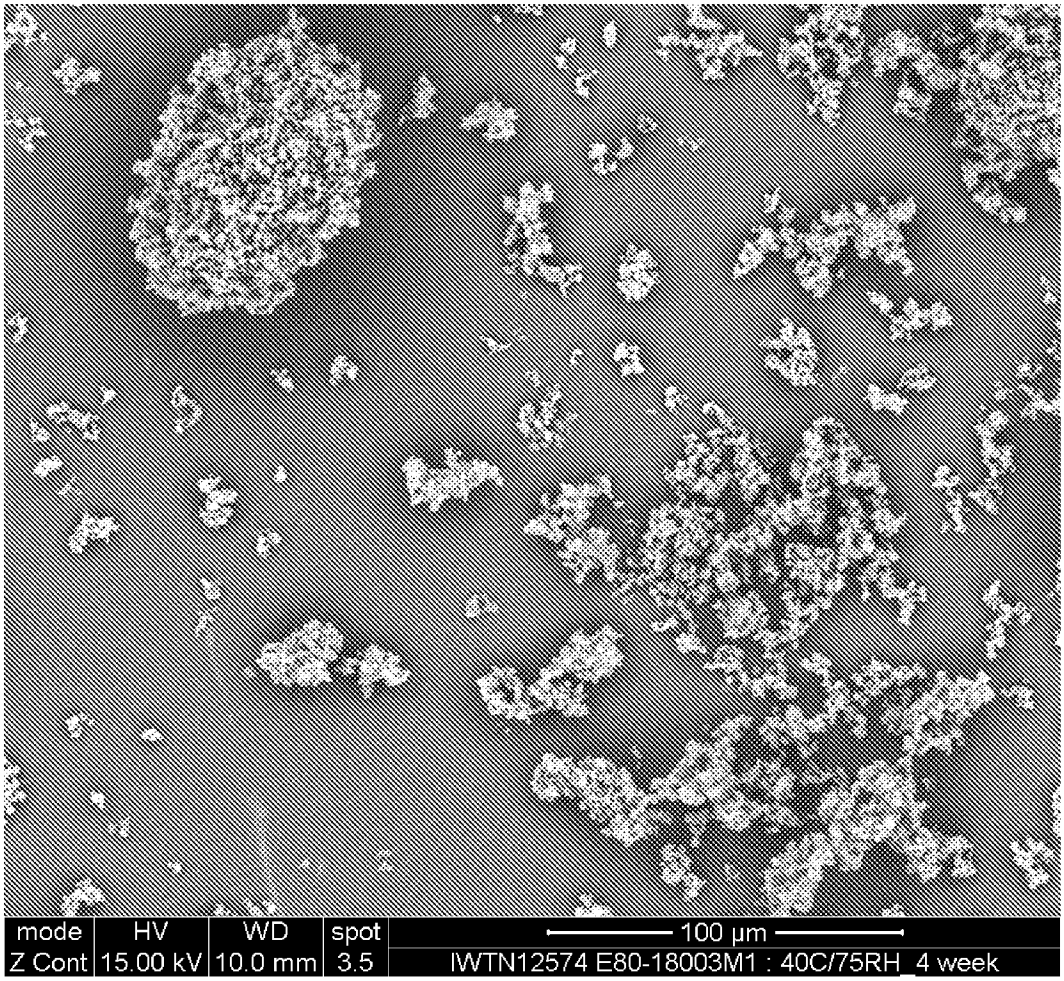

mode
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Z Cont
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10.0 mm
3.5
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FIGURE 3

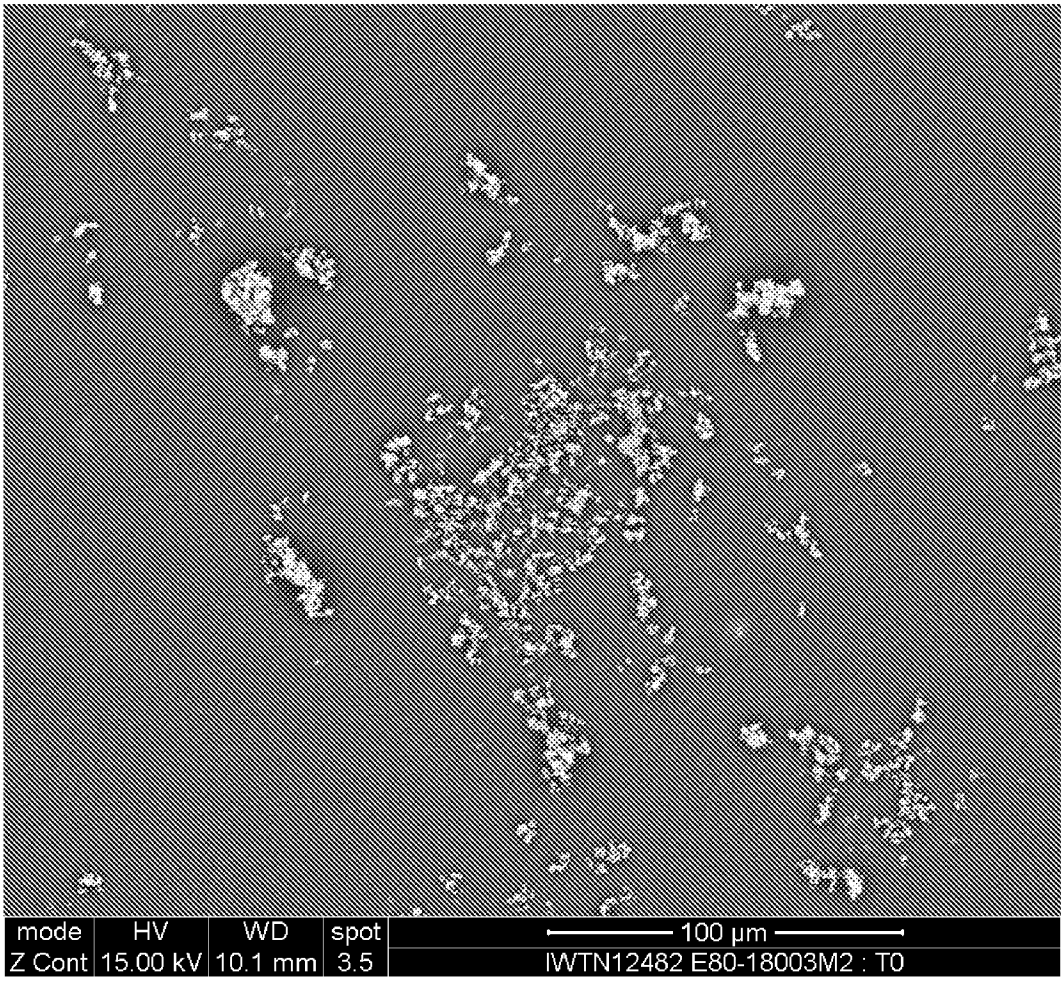

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Z Cont
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FIGURE 4

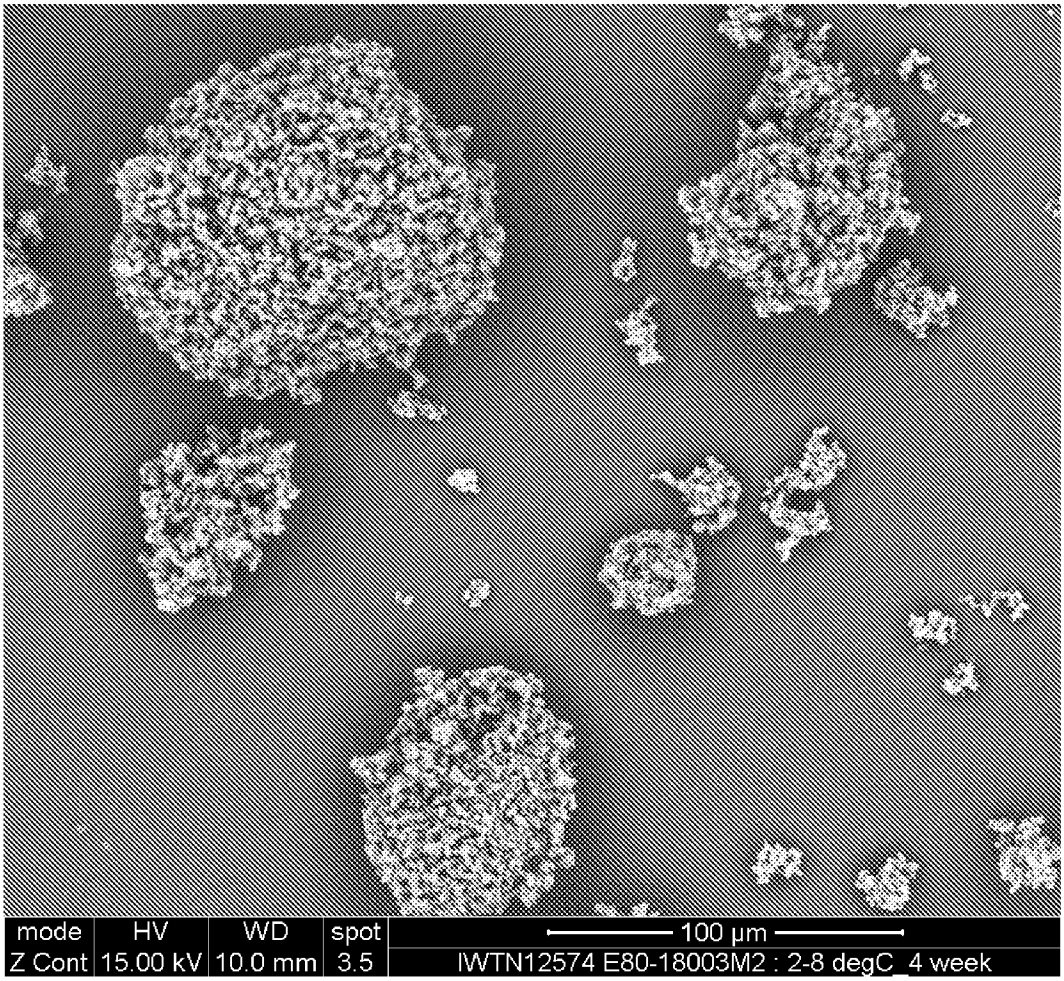

mode
HV
WD
spot
100 µm
Z Cont
15.00 kV
10.0 mm
3.5
IWTN12574 E80-18003M2 : 2-8 degC_4 week

FIGURE 5

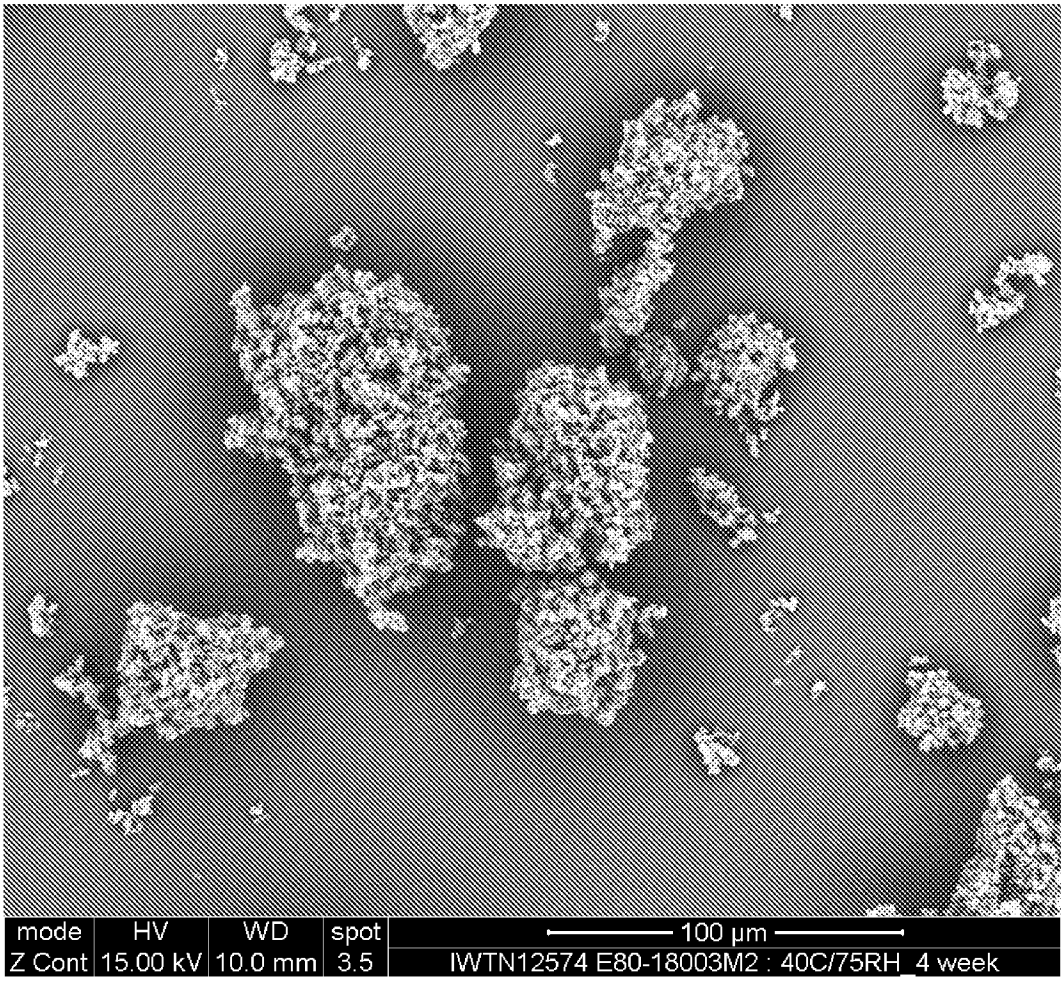
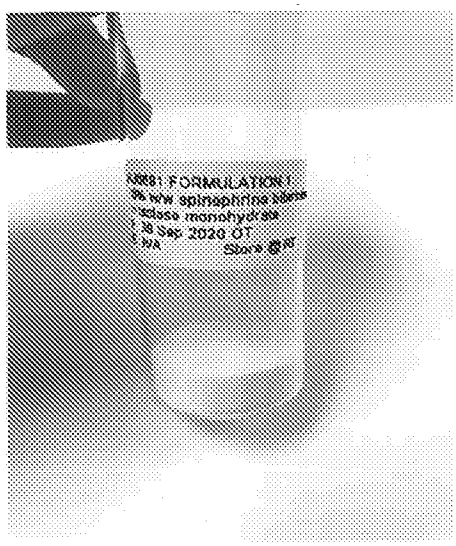

mode
HV
WD
spot
100 µm
Z Cont
15.00 kV
10.0 mm
3.5
IWTN12574 E80-18003M2 : 40C/75RH_4 week

FIGURE 6

A.



B.

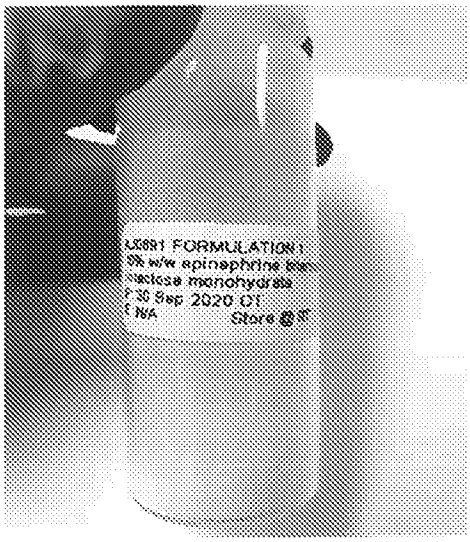
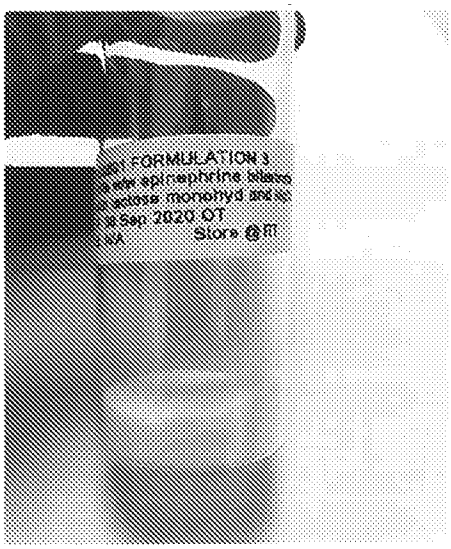


FIGURE 7

A.



B.

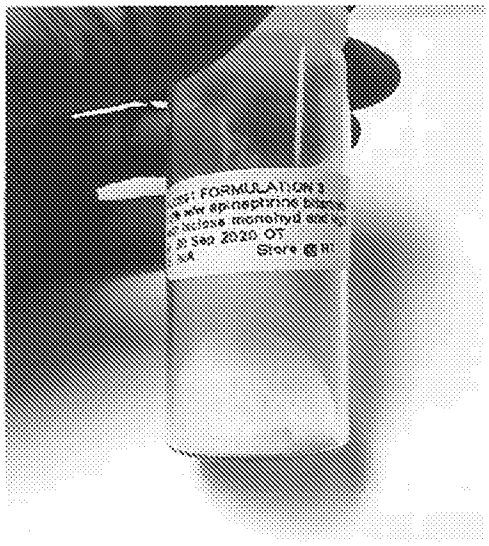


FIGURE 8

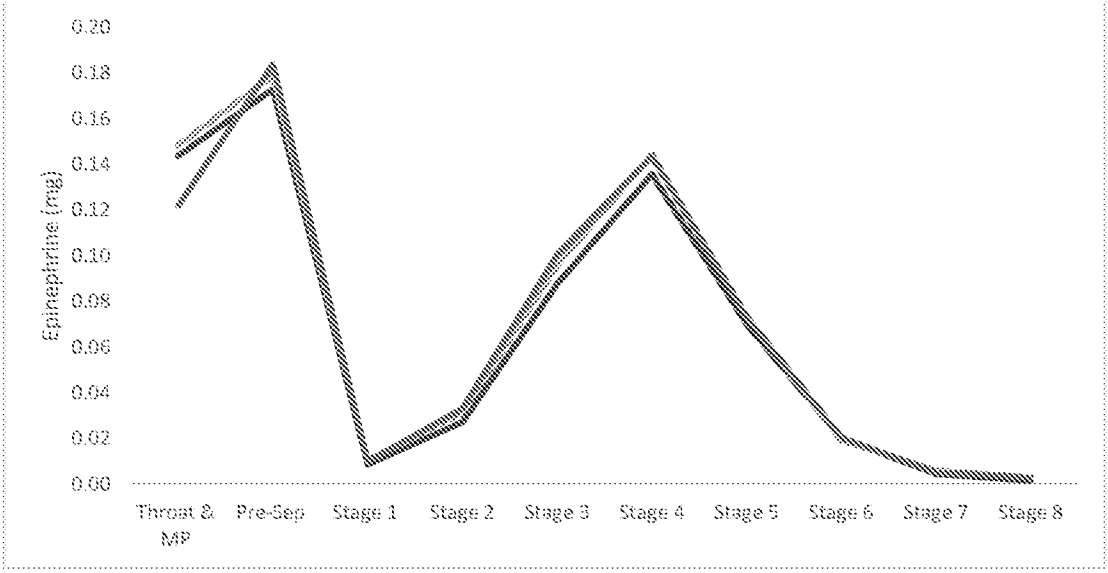

0.20
0.18
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Epinephrine (mg)
Throat & MP
Pre-Sep
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
Stage 8

FIGURE 9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2023/050756

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/137 (2006.01) A61K 9/00 (2006.01) A61K 9/14 (2006.01) A61K 47/26 (2006.01) A61P 37/08 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Epoque, STN; Databases: Epodoc, WPIAP, Medline, TXTE, HCAplus, Biosis, Embase; websites: Google.com; Keywords: epinephrine, adrenaline, norepinephrine, dopamine, 3-methoxytyramine, synephrine, octopamine, lactose, solid carrier, dry powder, inhaler, respiratory & like terms; IPC/CPC(s): A61K9/0075.

Inventor and Applicant name searches conducted on PatentScope, Espacenet, AusPat, PubMed and IP Australia internal databases.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 October 2023	05 October 2023

Name and mailing address of the ISA/AU	**Authorised officer**
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INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/AU2023/050756**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2021/0283050 A1 (Nasus Pharma Ltd.) 16 September 2021 Abstract; para. 0006, 0016, 0018, 0021, 0023, 0045, 0048-0053, 0095; Examples 1-3; Figs. 2-3; claims 1-23	1-20
X	US 2016/0220489 A1 (G2B Pharma Inc., et al.) 04 August 2016 Abstract; para. 0102, 0105, 0116, 0128, 0135, 0238, 0389-0392; Examples 2-3, 6-7; Test Article 8; Test Article-5; claims 91, 108, 127	1-20
X	US 2004/0076588 A1 (BATYCKY et al.) 22 April 2004 Abstract; para. 0010, 0040, 0090, Table A; Examples 1-16; claims 1-139	1-12, 14-20
X	US 2022/0087938 A1 (OREXO AB) 24 March 2022 Abstract; para. 0023, 0090, 0173, 0215, 0247; Examples 1-2; claims 1-26	1-12, 14-20
A	RAHIMPOUR, Y., et al., "Lactose Engineering for Better Performance in Dry Powder Inhalers", Advanced Pharmaceutical Bulletin (2012) vol. 2(2), pages 183-187 Whole document	
P,X	WO 2022/261453 A1 (BELHAVEN BIOPHARMA INC.) 15 December 2022 Abstract; para. 0003, 0008, 0171, 0205, 0219, 0230-0231; Tables 2-3; claims 1-20	1-12, 14-20

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2023/050756**

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/AU2023/050756**

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