more typically 2-5 µm). This size of particle is able to penetrate the lung on inhalation. However, such particles have a high surface energy and require a coarse carrier in order to be able to meter the formulation. The coarse carrier is typically lactose, usually in the form of α-lactose monohydrate.

The high surface energy of the active ingredient can affect the stability of the dry powder product over time.

Micronised fluticasone propionate is particularly sensitive to environmental conditions once the product has been removed from its protective packaging. For example, temperature and humidity have deleterious effects upon the aerodynamic particle size distribution (APSD) and fine particle fraction (FPF) of the dry powder formulation. For this reason, the fluticasone propionate mono product (ArmonAir® Respiclick, 55mcg) is typically marketed with a so-called "out-of-pouch shelf life" of 1 month and the fluticasone propionate mono product (ArmonAir®, 25mcg, Phase IIB) has been proven to have an "out-of-pouch shelf life" of 2 months.

In contrast, the albuterol product (ProAir Respiclick®, 90mcg) is more stable and has a longer out-of-pouch shelf life of 13 Months. Consequently, formulating combination products containing an ICS and a SABA is challenging. For example, the in-use stability of fluticasone propionate (when formulated with a SABA) would require extension to better match that of the SABA. Without this extension, the stability of the combination product is governed solely by the least stable active ingredient (i.e. for fluticasone propionate, ArmonAir® Respiclick).

There remains a need in the art for a dry powder inhalable formulation containing fluticasone propionate and albuterol sulfate which does not suffer the drawback of a short in-use shelf-life. There also remains a need in the art to treat asthma symptoms by way of a combination product of fluticasone propionate and albuterol sulfate.

Summary

In one aspect of the present disclosure, there is provided a dry powder inhalable formulation comprising fluticasone propionate, albuterol sulfate and α-lactose monohydrate, wherein the particle size distribution of the inhaled fluticasone propionate is d10 = 0.4-1.0 µm, d50 = 1.0-3.0 µm, d90 = 2.5-7.5 µm and NLT99% <10 µm.

In another aspect of the present disclosure, there is provided a use of a dry powder inhalable formulation disclosed herein in the manufacture of a medicament for the treatment of asthma or COPD.

In a further aspect of the present disclosure, there is provided a use of a dry powder inhalable formulation disclosed herein, in the manufacture of a medicament for the long-term treatment of

asthma and/or COPD and the treatment of acute exacerbations of asthma and/or COPD, wherein the formulation is to be administered as a maintenance dose for the long-term treatment of asthma and pro re nata (p.r.n.) as a rescue medication for the treatment of acute exacerbations of asthma.

In another aspect of the present disclosure, there is provided a process for preparing the dry powder inhalable formulation disclosed herein, comprising mixing fluticasone propionate, albuterol sulfate and α-lactose monohydrate to form the formulation.

In a further aspect of the present disclosure, there is provided a process for preparing a dry powder inhalable formulation, comprising the steps of:
(i) preparing a mixture of fluticasone propionate, albuterol sulfate and α-lactose monohydrate; and
(ii) conditioning the mixture.

In another aspect of the present disclosure, there is provided a product obtainable by the process disclosed herein.

In a further aspect of the present disclosure, there is provided a dry powder inhaler or a dry powder inhaler comprising a cyclone deagglomerator for breaking up agglomerates of the dry powder, containing the dry powder inhalable formulation disclosed herein.

In another aspect of the present disclosure, there is provided a use of albuterol sulfate to stabilise fluticasone propionate in a dry powder inhalation formulation.

In a further aspect of the present disclosure, there is provided a dry powder inhalable formulation disclosed herein, for use in therapy.

Description

Accordingly, the present invention provides a dry powder inhalable formulation comprising fluticasone propionate, albuterol sulfate and an α-lactose monohydrate carrier.

It has been suggested that albuterol sulfate has a stabilising effect on fluticasone propionate when formulated with an α-lactose monohydrate carrier. Formulation development work was carried out to increase the in-use shelf life of fluticasone propionate in combination with albuterol sulfate. The formulation was also developed to ensure that both molecules are compatible.
The formulation displays an advantageous stability profile, is resistant to degradation and demonstrates prolonged pharmaceutical performance and in-use shelf life (in comparison to the respective mono-products).

The invention will now be described in detail with reference to the accompanying drawings, in which:

Claims

1. A dry powder inhalable formulation comprising fluticasone propionate, albuterol sulfate and α-lactose monohydrate, wherein the particle size distribution of the inhaled fluticasone propionate is d10 = 0.4-1.0 µm, d50 = 1.0-3.0 µm, d90 = 2.5-7.5 µm and NLT99% <10 µm.

2. A dry powder inhalable formulation as claimed in claim 1, wherein the weight ratio of albuterol sulfate to fluticasone propionate is from 1.0-10.0 to 1.0, preferably from 2.0-5.0 to 1.0.

3. A dry powder inhalable formulation as claimed in any preceding claim, wherein the formulation does not include a ternary excipient.

4. A dry powder inhalable formulation as claimed in any preceding claim, wherein the formulation consists of fluticasone propionate, albuterol sulfate and α-lactose monohydrate.

5. Use of a~~A~~ dry powder inhalable formulation as claimed in any preceding claim in the manufacture of a medicament for ~~use in~~ the treatment of asthma or COPD.

6. Use of a~~A~~ dry powder inhalable formulation as claimed in claim 5, in the manufacture of a medicament for ~~use in~~ the long-term treatment of asthma and/or COPD and the treatment of acute exacerbations of asthma and/or COPD, wherein the formulation is to be administered as a maintenance dose for the long-term treatment of asthma and pro re nata (p.r.n.) as a rescue medication for the treatment of acute exacerbations of asthma.

7. The use~~A dry powder inhalable formulation~~ as claimed in claim 5 or 6, wherein the total ~~administered~~ daily dose of fluticasone propionate that is to be administered does not exceed 1,000 µg, and wherein the total ~~administered~~ daily dose of albuterol sulfate that is to be administered does not exceed 800 µg.

8. A process for preparing the dry powder inhalable formulation as claimed in any preceding claim, comprising mixing fluticasone propionate, albuterol sulfate and α-lactose monohydrate to form the formulation.

9. A process as claimed in claim 8, comprising the steps of:

(i) preparing a mixture of fluticasone propionate and α-lactose monohydrate to form a first blend;

(ii) preparing a mixture of albuterol sulfate and α-lactose monohydrate to form a second blend; and

(iii) mixing the first blend and the second blend to form the formulation.

10. The process as claimed in claim 9, further comprising step (iv), wherein step (iv) includes conditioning the formulation.

11. The process as claimed in claim 10, wherein step (iv) includes exposure of the formulation to 65%RH / 30°C for a duration of 21 to 36 days, or wherein step (iv) includes exposure of the formulation to 65%RH / 30°C for a duration of 28 to 35 days, or wherein step (iv) includes exposure of the formulation to 65%RH / 30°C for a duration of 28 days.

12. The process as claimed in claim 10 or 11, wherein the formulation is loaded into a formulation reservoir of a dry powder inhaler, and the dry powder inhaler is placed on a tray prior to the performance of step (iv).

13. The process as claimed in claim 10 or 11, wherein the formulation is loaded into a formulation reservoir of a dry powder inhaler, and the dry powder inhaler is placed on a tray and the inhaler and tray are wrapped with a polyethylene wrap prior to the performance of step (iv).

14. A product obtainable by the process as claimed in any one of claims 8 to 13.

15. A process for preparing a dry powder inhalable formulation, comprising the steps of:

(i) preparing a mixture of fluticasone propionate, albuterol sulfate and α-lactose monohydrate; and

(ii) conditioning the mixture.

16. The process as claimed in claim 15, wherein step (ii) includes exposure of the formulation to 65%RH / 30°C for a duration of 21 to 36 days, or wherein step (ii) includes exposure of the formulation to 65%RH / 30°C for a duration of 28 to 35 days, or wherein step (ii) includes exposure of the formulation to 65%RH / 30°C for a duration of 28 days.

17. The process as claimed in claim 15 or 16 wherein the formulation is loaded into a formulation reservoir of a dry powder inhaler, and the dry powder inhaler is placed on a tray prior to the performance of step (ii).

18. The process as claimed in claim 15 or 16, wherein the formulation is loaded into a formulation reservoir of a dry powder inhaler, and the dry powder inhaler is placed on a tray and the inhaler and tray are wrapped with a polyethylene wrap prior to the performance of step (ii).

19. A product obtainable by the process as claimed in any one of claims 15 to 18.

20. A dry powder inhaler or a dry powder inhaler comprising a cyclone deagglomerator for breaking up agglomerates of the dry powder, containing the dry powder inhalable formulation as claimed in any one of claims 1-7, 14 or 19.

21. The inhaler as claimed in claim 20, wherein the deagglomerator comprises:
an inner wall defining a swirl chamber extending along an axis from a first end to a second end;
a dry powder supply port in the first end of the swirl chamber for providing fluid communication between a dry powder delivery passageway of the inhaler and the first end of the swirl chamber;
at least one inlet port in the inner wall of the swirl chamber adjacent to the first end of the swirl chamber providing fluid communication between a region exterior to the deagglomerator and the first end of the swirl chamber;
an outlet port providing fluid communication between the second end of the swirl chamber and a region exterior to the deagglomerator; and
vanes at the first end of the swirl chamber extending at least in part radially outwardly from the axis of the chamber, each of the vanes having an oblique surface facing at least in part in a direction transverse to the axis; whereby a breath induced low pressure at the outlet port causes air flows into the swirl chamber through the dry powder supply port and the inlet port.

22. The inhaler as claimed in claim 20 or 21, comprising:
a sealed reservoir including a dispensing port;
a channel communicating with the dispensing port and including a pressure relief port;
a conduit providing fluid communication between an interior of the sealed reservoir and the pressure relief port of the channel; and a cup assembly movably received in the channel and including, a recess adapted to receive formulation when aligned with the dispensing port, a first sealing surface adapted to seal the dispensing port when the recess is unaligned with the dispensing port, and a second sealing surface adapted to sealing the pressure relief port when the recess is aligned with the dispensing port and unseal the pressure relief port when the recess is unaligned with the dispensing port.

23. Use of albuterol sulfate to stabilise fluticasone propionate in a dry powder inhalation formulation.

24. A dry powder inhalable formulation as claimed in claim 1, wherein the particle size distribution of the inhaled albuterol sulfate is d10 = 0.4-1.0 µm, d50 = 1.0-3.0 µm, d90 = 2.5-9.0 µm and NLT99% <10 µm.

25. A dry powder inhalable formulation as claimed in claim 1 or 24, wherein the particle size distribution of the inhaled α-lactose monohydrate is d10 = 10-25 µm, d50 = 85-105 µm, d90 = 140-180 µm, NLT99% <300 µm and 1.5-8.5% <10 µm, or d10 = 19-43 µm, d50 = 50-65 µm, d90 = 75-106 µm, NLT99% <300 µm and 1.5-2-5% <10 µm.

26. A dry powder inhalable formulation as claimed in claims 1 – 4, for use in therapy.