

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1417PC00	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2015/070660	International filing date (<i>day/month/year</i>) 09.09.2015	Priority date (<i>day/month/year</i>) 09.09.2014	
International Patent Classification (IPC) or national classification and IPC INV. A61K9/00			
Applicant Vectura Limited			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>8</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (<i>sent to the applicant and to the International Bureau</i>) a total of <u>8</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☒ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application			
Date of submission of the demand 07.07.2016		Date of completion of this report 09.09.2016	
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Schwald, Claudia Telephone No. +31 70 340-3381	



Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-50 as originally filed

Claims, Numbers

1-36 filed with the letter of 07-07-2016

Drawings, Sheets

1/23-23/23 as originally filed

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2015/070660

6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 23.08.2016 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-36</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-36</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-36</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Amendments

The amendment filed with the International Bureau under Article 19(1) PCT do not extend beyond the application as originally filed and are thus considered allowable under Article 19(2) PCT.

2 Medical use

a. Claim 35 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

b. Claim 32 comprises an option relating to a "method according to preceding claims for use in treating" which is not worded in a proper medical use claim as substance/ composition for use in a treatment as indicated above.

3 Documents

a. Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1 US 2014/080890 A1 (SNAPE SUSAN [GB] ET AL) 20 March 2014
(2014-03-20)

D2 US 2008/063719 A1 (MORTON DAVID [GB] ET AL) 13 March 2008
(2008-03-13)

4 Novelty

a. The subject-matter of claims 1-36 is considered to be new (Article 33(2) PCT).

b. Document D1 discloses (D1, paragraphs [0013], [0015], [0028] - [0029], [0057] - [0060], [0064]; paragraphs [0092] - [0109], [0135], [0139]; examples 1, 2): Stabilized, co-jet milled product comprising glycopyrrolate and magnesium stearate, which is subsequently blended with lactose and filled into capsules for use in dry powder inhalers. However D1 does not disclose that the co-jet milling takes place with a) milling gas of at up to 20% relative humidity and b) in that a conditioning step of the micronized particles is added at temperatures between 5 to 88°C and c) in that the relative humidity is 10-95%. The resulting (amorphous, partly re-crystallized) product is characterized by smaller particle sizes (D_{10} , D_{50} and D_{90}) compared to those being co-jet milled at higher relative humidity (30% RH), that smaller particle size being maintained during the conditioning step (Figures 41, 43-44, 46-47, 49-50, 52-56 and p.46, §2, p.49, §2 and tables 5-6).

Therefore D1 does not take away Novelty of claims 1-36.

c. Document D2 discloses (D2, paragraphs [0001] - [0002], [0011], [0016] - [0018]; paragraphs [0029], [0035] - [0036], [0048], [0056]; paragraph [0057]; examples 4, 7, 8): Stabilized compositions comprising glycopyrrolate for use in chronic obstructive pulmonary diseases. Specifically compositions comprising glycopyrrolate and magnesium stearate by high shear mixing and mechano-fusion of already micronized glycopyrrolate with magnesium stearate. Relative humidity during mechano-fusion is not indicated, but [0035] states that micronization should preferably be carried out at 30-70%RH for avoiding the formation of amorphous material. Preferably a conditioning step of at least 10 minutes on trays at humid conditions of 30-100RH and 5-90°C follows the micronization in order to reduce surface non-crystalline material present (D2, [0160-0167 and 0036]). An average fine particle fraction (less than 5 micron) was calculated of 40%.

However D2 does not disclose that the co-jet milling takes place with a) milling gas of at up to 20% relative humidity on *un*micronized glycopyrrolate. The resulting (amorphous, partly re-crystallized) product is characterized by smaller particle sizes (D_{10} , D_{50} and D_{90}) compared to those being co-jet milled at higher relative humidity (30% RH), that smaller particle size being maintained during the conditioning step (Figures 41, 43-44, 46-47, 49-50, 52-56 and p.46, §2 and tables 5-6).

Therefore D2 does not take away Novelty of claims 1-36.

5 Inventive step

a. The subject-matter of claims 1-36 seems to be inventive over the prior art (Article 33(3) PCT).

b. The document which is the closest prior art for claim 1 is document D1, since it relates to the same technical field of a process of preparing co-jet-milled glycopyrrolate and magnesium stearate.

Said D1 discloses (D1, paragraphs [0013], [0015], [0028] - [0029], [0057] - [0060], [0064]; paragraphs [0092] - [0109], [0135], [0139]; examples 1, 2): Stabilized, co-jet milled product comprising glycopyrrolate and magnesium stearate, which is subsequently blended with lactose and filled into capsules for use in dry powder inhalers.

The subject matter of claim 1 therefore differs from this known D1 in that it specifies that the co-jet milling takes place with a) milling gas of at up to 20% relative humidity and b) in that a conditioning step of the micronized particles is added at temperatures between 5 to 88°C at a humidity of 10-95%RH.

The effect related to these differences can be considered as

a) the resulting product is characterized by smaller particle sizes (D_{10} , D_{50} and D_{90}) compared to those being co-jet milled at higher relative humidity (30% RH).

b) the effect of the conditioning step can be considered as a smaller particle size which is maintained during the conditioning step (Figures 41, 43-44, 46-47, 49-50, 52-56 and p.46, §2, p.49, §2 and tables 5-6). This effect has been credibly solved for the conditioning conditions as outlined above.

The problem to be solved by the present invention may therefore be regarded as provision of a process leading to smaller particle sizes and a different particle size distribution which remains stable throughout the conditioning process.

The solution proposed in claim 1 of the present application can be considered as involving an inventive step (Articles 33(3)PCT) for the following reasons:

No document of the prior art discloses or suggests to apply a relative humidity of less than 20% during co-jet milling of glycopyrrolate and magnesium. D1 and D2 mention both moisture as a problem for the active and the amount of formation of amorphous material, but they suggest both to apply 30-70% RH during micronization. Also no document of the prior art suggests to lower the humidity at this stage in order to solve the problem of achieving smaller particle sizes or a different particle size distribution, which could then be maintained by a further conditioning step. Even though conditioning was principally known from D2, this was applied to remove or reduce

amorphous material and encourage re-crystallization of the active without formation of hard agglomerates (D2, [0036]). D2 does not hint or suggest that the small particle size distribution can be retained by conditioning.

For these reasons is the subject matter of claim 1 considered as being not obvious and as inventive in the meaning of Article 33(3) PCT.

c. The same positive assessment applies mutatis mutandis to method claim 27.

d. Claims 28, 34 and 32 and dependent claims:

d.1. The document which is the closest prior art for the product obtainable by the method (claim 28) is D1, since it relates to the same technical field of a products obtained by a similar process of preparing co-jet-milled glycopyrrolate and magnesium stearate.

The subject matter of claim 28 therefore differs from this known D1 in that it relates to a product prepared by a different process.

The effect of this different process can be considered as

a) smaller particle sizes and a narrower particle size distribution (D_{10} , D_{50} and D_{90}) compared to those being co-jet milled at higher relative humidity (30% RH) and

b) the effect of the conditioning step can be considered as a smaller particle size which is maintained during the conditioning step (Figures 41, 43-44, 46-47, 49-50, 52-56 and p.46, §2, p.49, §2 and tables 5-6).

The problem to be solved by the present invention may therefore be regarded as provision of a product which has smaller particle sizes and a narrower particle size distribution which is maintained during conditioning.

The solution proposed in claim 28 of the present application can be considered as involving an inventive step (Articles 33(3)PCT) for the following reasons:

No document of the prior art discloses or suggests to apply a process with a relative humidity of less than 20% during co-jet milling of glycopyrrolate and magnesium in order to achieve the relevant smaller particles and narrower particle size distribution which is maintained during conditioning.

D1 and D2 mention both moisture as a problem *for the active and the the amount of formation of amorphous material*, but not for particle size, and they suggest both to apply 30-70% RH and not 20% during micronization.

Even though conditioning was principally known from D2, this was applied to remove or reduce amorphous material and encourage re-crystallization of the active without formation of hard agglomerates (D2, [0036]). D2 does not hint or suggest that the small particle size distribution can be retained by conditioning.

For these reasons is the subject matter of claim 28, the DPI comprising it (claim 34) as well as a kit (claim 36) and its medical use as of claim 32 as well as the dependent claims considered inventive in the meaning of Article 33(3) PCT.

6 Industrial applicability

The subject matter of claims 1-36 appears to be industrially applicable in the meaning of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

1. Further remarks

- a. Terms like "optionally for use" as of claim 28 are interpreted as introducing no limitation to the scope of the claim.
- b. The vague and imprecise statement in the description on page 32 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity of the claims (Article 6 PCT) when used to interpret them.

Re Item VIII

Certain observations on the international application

1. Clarity

- a. The application does not meet the requirements of Article 6 PCT, because the subject matter of claim 25 is not clear:

The term bracketed terms e.g. "(salbutamol)" and the like in claim 25 renders its scope unclear in the meaning of Article 6 PCT, since it is not evident to the person skilled whether the content belongs to the scope of the claim or not.

The European Patent Office
as Receiving Office and International Searching Authority
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk – Pays Bas
Netherlands

7 July 2016

Dear Sirs

Response to Written Opinion for International Patent Application PCT/EP2015/070660
Claiming priority from European Patent Application Number 14184164.3
Formulation, Method and Apparatus
In the name of Vectura Limited
Our Reference: P1417PC00

In reply to the Written Opinion of the International Searching Authority dated 26th November 2015, we hereby file a Demand for further International Preliminary Examination under Chapter II of the Patent Cooperation Treaty and pay the associated fees.

We file herewith amended claims 1 to 36 to replace the claims presently on file. Both clean and tracked changes versions of the claim amendments are enclosed.

Amendments

Claim 1 has been amended to specify the range of conditioning humidity and now reads as follows:

*A method of making a dry powder formulation, the method comprising co-jet milling unmicronised glycopyrrolate and magnesium stearate with milling gas having a humidity below 20% Relative Humidity to produce micronized composite particles, wherein the micronized composite particles are then subjected to a conditioning step which includes exposure of the micronized composite particles to humidity **in the range of 10%-95% Relative Humidity** at temperatures between 5°C to 88°C for at least 60 minutes.*

Basis for this amendment is provided in claim 5 of the application as filed, where the conditioning humidity is defined in a broadest sense as 10%-95% RH. The term "RH" found in original Claim 5 has been written in full as "Relative Humidity" in amended Claim 1.

For consistency Claim 27 has also been amended to specify the range of conditioning humidity and now reads as follows:

*A method of making a dry powder formulation, the method comprising co-jet milling unmicronised glycopyrrolate and magnesium stearate with milling gas having a humidity below 20% Relative Humidity to produce micronized composite particles, wherein the micronized composite particles are then subjected to a conditioning step which includes exposure of the micronized composite particles to humidity **in the range of 10%-95% Relative Humidity** at temperatures between 5°C to 88°C for at least 10 minutes.*

Basis for this feature is provided on page 4 lines 23 of the application as filed, where the conditioning humidity is defined in a broadest sense as 10%-95% RH.

Novelty (Article 33(2) PCT)

The Written Opinion acknowledged the novelty of original Claims 1-36 because D1 and D2 do not disclose a jet milling gas having humidity below 20% Relative Humidity. Consequently the amended claims are also novel.

Inventive Step (Article 33(3) PCT)

The Written Opinion considered that original Claim 5 is inventive. Since the amended independent claims now specify that the conditioning humidity is in the range of 10%-95% RH, we submit that all claims are inventive.

General

The outcome of International Preliminary Examination under Chapter II is now eagerly awaited. Should the Examiner consider that a telephone call would help resolve any remaining matters, the Examiner is asked to contact the undersigned on +44 1249 667700.

Yours faithfully

[Signed electronically]

Chris Clarke
Vectura Limited

Encl. Claims (Amended Clean)
 Claims (Amended Marked-up)

Claims

1. A method of making a dry powder formulation, the method comprising co-jet milling unmicronised glycopyrrolate and magnesium stearate with milling gas having a humidity
5 below 20% Relative Humidity to produce micronized composite particles, wherein the micronized composite particles are then subjected to a conditioning step which includes exposure of the micronized composite particles to humidity in the range of 10%-95% Relative Humidity at temperatures between 5°C to 88°C for at least 60 minutes.
- 10 2. The method according to claim 1, wherein the conditioning is initiated within 30 minutes of completing the milling, within 25 minutes, within 20 minutes, within 15 minutes, preferably within 10 minutes, more preferably within 5 minutes, most preferably immediately after completing the co-jet milling of the glycopyrrolate and magnesium stearate.
- 15 3. The method according to claims 1 to 2, wherein the fraction of the conditioned co-jet milled formulation which is greater than 10 µm is less than 20% by volume or mass, preferably wherein the fraction which is greater than 10 µm is less than 15% by volume or mass, more preferably wherein the fraction which is greater than 10 µm is less than 10% by volume or mass, or more preferably wherein the fraction which is greater than 10 µm is
20 less than 5% by volume or mass, immediately after the co-jet milling and after the conditioning process as suitably determined by a Malvern Mastersizer or similar laser diffraction equipment.
- 25 4. The method according to claims 1 to 3, wherein the magnesium stearate is co-jet milled in an amount of from 1 to 25 % (w/w), more preferably from 2 to 20 % (w/w), more preferably 3 to 15 % (w/w), more preferably 4 to 10 % (w/w) but most preferably from 5 to 7.5 % (w/w) magnesium stearate by weight of the co-jet milled combination of glycopyrrolate and magnesium stearate.
- 30 5. The method according to claims 1 to 4, wherein the conditioning humidity is 30-90% RH, 45-90% RH or 50-88% RH or more preferably 60-87% RH.
- 35 6. The method according to claim 5, wherein the method further comprises subjecting the micronized composite particles to an ventilating atmosphere having relative humidity in the range of 10%-95% RH, preferably 30-90% RH, 45-90% RH or 50-88% RH or more preferably 60-87%, preferably wherein the atmosphere is air.

7. The method according to claim 6, wherein ventilating atmosphere passes over and through a powder bed comprising micronized composite particles at a rate of less than $100 \text{ cm}^3/\text{s}$, less than $10 \text{ cm}^3/\text{s}$, less than $5 \text{ cm}^3/\text{s}$, less than $2 \text{ cm}^3/\text{s}$, less than $1 \text{ cm}^3/\text{s}$, preferably less than $0.8 \text{ cm}^3/\text{s}$, preferably less than $0.6 \text{ cm}^3/\text{s}$, preferably less than $0.4 \text{ cm}^3/\text{s}$, preferably less than $0.2 \text{ cm}^3/\text{s}$, preferably less than $0.1 \text{ cm}^3/\text{s}$, more preferably about $0.001 \text{ cm}^3/\text{s}$.
8. The method according to claim 7, wherein the volume ratio of ventilating atmosphere to poured bulk powder is more than 1:1, preferably more than more than 10:1, preferably more than more than 100:1, preferably more than more than 1,000:1, preferably more than 10,000:1, preferably more than 100,000:1, preferably more than 1,000,000:1, more preferably more than 10,000,000:1.
9. The method according to claims 1 to 8, wherein the conditioning step is carried out for at least 75 minutes, preferably for at least 85 minutes, preferably for at least 1.5 hours, at least 2 hours, at least 3 hours, at least 5 hours, at least 6 hours, at least 12 hours, at least 18 hours, preferably at least 24 hours, preferably for at least 36 hours or more preferably for at least 48 hours.
10. The method according to claims 1 to 9, wherein the conditioning step includes exposing the micronized composite particles to a temperature in the range from 10°C to 50°C , more preferably 24°C to 50°C .
11. The method according to claims 1 to 10, wherein the micronized composite particles are blended with a carrier, preferably lactose, more preferably anhydrous lactose, more preferably alpha-lactose monohydrate, optionally after the conditioning step.
12. The method according to claim 11, wherein the micronized composite particles are present in an amount of less than 5%, less than 4%, less than 3%, preferably less than 2%, preferably less than 1%, preferably less than 0.75%, preferably less than 0.5% by weight of the formulation.
13. The method according to claims 1 to 12, wherein the conditioning step takes place by distributing the micronized composite particles on a surface, optionally wherein the conditioning step takes place on a tray.

14. The method according to claims 1 to 13, wherein the conditioning step involves exposing the micronized composite particles to the humidity for sufficient time for amorphous glycopyrrolate to re-crystallise after co-jet milling, as determined by dynamic vapour sorption.
15. The method according to claims 1 to 14, wherein the conditioning step involves powder agitation, optionally wherein the agitation is intermittent powder agitation.
16. The method according to claim 15, wherein the powder agitation takes places within 30 minutes of completing the milling, within 25 minutes, within 20 minutes, within 15 minutes, preferably within 10 minutes, more preferably within 5 minutes, most preferably immediately after completing the milling of the glycopyrrolate and magnesium stearate.
17. The method according to claims 15 to 16, wherein the powder agitation involves a fluidised bed.
18. The method according to claims 15 to 16, wherein the powder agitation is provided by a Resonance Acoustic Mixer.
19. The method according to claims 1 to 18, wherein the milling gas has a humidity preferably below 15% Relative Humidity, preferably below 10% Relative Humidity, preferably below 5% Relative Humidity, more preferably below 2.5% Relative Humidity.
20. The method according to claims 1 to 19, wherein the milling gas is preferably air, nitrogen or helium or combination thereof.
21. The method according to claim 1 to 20, wherein the co-jet milling is carried out at an averaged powder feed rate of between 0.1 and 50 g/min, preferably at a feed rate of between 0.5 and 40 g/min, preferably at a feed rate of between 1 and 30 g/min, preferably at a feed rate of between 1.5 and 25 g/min, preferably at a feed rate of between 0.1 and 20 g/min, preferably at a feed rate of between 0.5 and 15 g/min, preferably at a feed rate of between 1 and 10 g/min, preferably at a feed rate of between 1.5 and 5 g/min.
22. The method according to claim 1 to 21, wherein the co-jet milling is carried out at an inlet pressure of between 3 and 12 bar, preferably at an inlet pressure of between 4 and 10 bar, or more preferably at an inlet pressure of between 5 and 9 bar.

23. The method according to claim 1 to 22, wherein the co-jet milling is carried out at a grinding pressure of more than 2 bar below the inlet pressure.
24. The method according to claim 23, wherein the grinding pressure is carried out at
5 between 1 and 10 bar, preferably at a pressure of between 2 and 8 bar, or more preferably at a pressure of between 3 and 7 bar.
25. The method according to any preceding claims, wherein the formulation further comprises a beta-2 adrenoceptor agonist, preferably wherein the beta-2 adrenoceptor agonist is
10 albuterol (salbutamol), metaproterenol, terbutaline, salmeterol, fenoterol, procaterol, preferably, formoterol, carmoterol and pharmaceutically acceptable salts thereof, more preferably wherein the beta-2 adrenoceptor agonist is (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]- 8-hydroxy-1H-quinolin-2-one maleate.
26. The method according to any preceding claims, wherein the formulation comprises
15 glycopyrrolate, indacaterol and mometasone, preferably glycopyrronium bromide, indacaterol maleate and mometasone furoate.
27. A method of making a dry powder formulation, the method comprising co-jet milling
20 unmicronised glycopyrrolate and magnesium stearate with milling gas having a humidity below 20% Relative Humidity to produce micronized composite particles, wherein the micronized composite particles are then subjected to a conditioning step which includes exposure of the micronized composite particles to humidity in the range of 10%-95% Relative Humidity at temperatures between 5°C to 88°C for at least 10 minutes.
28. A formulation comprising co-jet milled and then co-conditioned particles comprising
25 glycopyrrolate and magnesium stearate obtained or obtainable by a method according to any preceding claim, optionally for use in a treatment of a respiratory disease, or for use in the preparation of a medicament for the treatment of a respiratory disease.
29. A formulation or a method as claimed in any preceding claim wherein the glycopyrrolate is
30 a racemate.
30. A formulation or a method as claimed in any preceding claim wherein the glycopyrrolate is
35 a single enantiomer.

31. A formulation or a method as claimed in in any preceding claim, wherein the magnesium stearate forms a coating on the surface of the glycopyrrolate particles as measured by energy-dispersive X-ray spectroscopy.

5 32. A formulation or a method according to any preceding claims for use in treatment of a respiratory condition.

33. A formulation or a method according to any preceding claims, wherein the span of the co-jet milled and co-conditioned glycopyrrolate and magnesium stearate agent is less than
10 150, more preferably less than 125, more preferably less than 100, or more preferably less than 50 prior to blending with carrier particles.

34. A dry powder inhaler containing a formulation comprising co-jet milled and then co-conditioned particles comprising glycopyrrolate and magnesium stearate as claimed in
15 any one of claims 28 to 33.

35. Use of co-jet milled and co-conditioned particles according to any claims 28-34 for the treatment of a respiratory disease, preferably wherein the respiratory disease is chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis (CF) and related airway
20 diseases.

36. A pharmaceutical kit comprising micronized composite particles according to claims 1-24 and a further active according to claim 25, in combined or separate unit dosage forms, said forms being suitable for administration of the co-jet milled glycopyrrolate and the
25 further active in effective amounts, optionally together with one or more inhalation devices for administration of both actives.

30

REIVINDICACIONES

1. Un método de fabricación de una formulación de polvo seco; el método comprende co-triturar en molino de chorro el glicolpirrolato no micronizado y el estearato de magnesio con gas para molienda el cual tiene una humedad por debajo del 20% de humedad relativa para producir partículas compuestas micronizadas, en las que las partículas compuestas micronizadas se someten entonces a una etapa de acondicionamiento que incluye la exposición de las partículas compuestas micronizadas a condiciones húmedas con temperaturas entre los 5 ° C y 88 ° C al menos durante 60 minutos.
2. El método conforme a la reivindicación 1, en el que el acondicionamiento se inicia dentro de los 30 minutos de completar la molienda, dentro de los 25 minutos, dentro de los 20 minutos, dentro de los 15 minutos, preferiblemente dentro de los 10 minutos, más preferiblemente dentro de los 5 minutos, lo más preferiblemente inmediatamente después de completar la co-tritura en molino de chorro del glicopirrolato y del estearato de magnesio.
3. El método conforme a las reivindicaciones 1 a 2, en el que la fracción de la formulación co-triturada en molino de chorro acondicionada, que es superior a 10 µm es menos del 20% en volumen o en masa, preferiblemente en la que la fracción que es superior a 10 µm es menos del 15% en peso o en masa, más preferiblemente en la que la fracción que es superior a 10 µm es menos del 10% en volumen o masa, o más preferiblemente en la que la fracción que es superior a 10 µm es menos del 5% en volumen o masa, inmediatamente después de co-triturar en molino de chorro y después del proceso de acondicionamiento como se determina adecuadamente por un equipo Malvern Mastersizer o un equipo de difracción láser similar.
4. El método conforme a las reivindicaciones 1 a 3, en donde el estearato de magnesio es co-triturado en molino de chorro en una cantidad de 1 a 25% (m/m), más preferiblemente desde 2 a 20 % (m/m), más preferiblemente 3 a 15% (m/m), más preferiblemente 4 a 10% (m/m) pero más preferiblemente desde 5 a 7.5% (m/m) estearato de magnesio por el peso de la combinación co-triturada en molino de chorro del glicopirrolato y el estearato de magnesio.
5. El método conforme a las reivindicaciones 1 a 4, en donde la humedad de acondicionamiento está en el intervalo 30-90% de HR, 45-90% de HR o 50-88% de HR o más preferiblemente 60-87% de HR.
6. El método conforme a la reivindicación 5, en donde el método además comprende el someter partículas compuestas micronizadas a una atmósfera de ventilación que tiene una humedad relativa en el intervalo de 10% -95% de HR, preferiblemente 30-90% de HR, 45-90% de HR o 50- 88% HR o más preferiblemente 60-87%, preferiblemente en el que la atmósfera es aire.
7. El método conforme a la reivindicación 6, en el que la atmósfera de ventilación pasa sobre y través de una cama de polvo que comprende partículas compuestas a micronizadas a una tasa de menos de 100 cm³/s, menos de 10 cm³/s, menos de 5 cm³/s, menos de 2 cm³/s, menos de 1 cm³/s, preferiblemente menos de 0,8 cm³/s,

- preferiblemente menos de 0,6 cm³/s, preferiblemente menos de 0,4 cm³/s, preferentemente menos de 0,2 cm³/s, preferentemente menos de 0,1 cm³/s, más preferiblemente 0,001 cm³/s aproximadamente.
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8. El método conforme a la reivindicación 7, en el que la relación en volumen de la atmósfera de ventilación al polvo a granel vertido es más de 1: 1, preferiblemente más de 10: 1, preferiblemente más de 100: 1, preferiblemente más de 1.000:1, preferiblemente más de 10.000: 1, preferiblemente más de 100.000: 1, preferiblemente más de
- 15 1.000.000: 1, más preferiblemente más de 10.000.000: 1.
9. El método conforme a las reivindicaciones 1 a 8, en el que la etapa de acondicionamiento se lleva a cabo durante al menos 75 minutos, preferiblemente durante al menos 85 minutos, preferiblemente durante al menos 1,5 horas, al menos 2 horas, al menos 3 horas, al menos 5 horas, al menos 6 horas, al menos 12 horas, al menos
- 20 18 horas, preferiblemente al menos 24 horas, preferiblemente durante al menos 36 horas o más preferiblemente durante al menos 48 horas.
10. El método conforme a las reivindicaciones 1 a 9, en el que la etapa de acondicionamiento incluye la exposición de las partículas de material compuesto micronizado a una temperatura en el intervalo de 10°C a
- 25 50°C, más preferiblemente de 24°C a 50°C.
11. El método conforme a las reivindicaciones 1 a 10, en el que las partículas de compuestas micronizadas se mezclan con un portador, preferiblemente la lactosa, más preferiblemente lactosa anhidra, más preferiblemente monohidrato de alfa-lactosa, opcionalmente después de la etapa de acondicionamiento.
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12. El método conforme a la reivindicación 11, en el que las partículas compuestas micronizadas están presentes en una cantidad de menos de 5%, menos de 4%, menos de 3%, preferiblemente menos de 2%, preferiblemente menos de 1%, preferiblemente menos de 0,75%, preferiblemente menos de 0,5% en peso de la formulación.
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13. El método conforme a a las reivindicaciones 1 a 12, en el que la etapa de acondicionamiento ocurre al distribuir las partículas compuestas micronizadas sobre una superficie, opcionalmente en donde la etapa de acondicionamiento ocurre sobre una bandeja.
- 5 14. El método conforme a las reivindicaciones 1 a 13, en el que la etapa de acondicionamiento implica exponer las partículas de material compuesto micronizado a la humedad durante suficiente tiempo para que el glicopirrolato amorfo vuelva a cristalizar después de la co-tritura en molino de chorro, según se determina por la sorción dinámica del vapor.
- 10 15. El método según las reivindicaciones 1 a 14 en el que la etapa de acondicionamiento implica la agitación del polvo, opcionalmente en donde la agitación es una agitación del polvo intermitente.

16. El método conforme a la reivindicación 15, en el que la agitación del polvo ocurre dentro de los 30 minutos siguientes a la finalización de la molienda, dentro de los 25 minutos, dentro de los 20 minutos, dentro de los 15 minutos, preferiblemente dentro de los 10 minutos, más preferiblemente dentro de los 5 minutos, lo más
- 15 preferiblemente inmediatamente después de la finalización de la molienda del glicopirrolato y el estearato de magnesio.
17. El método conforme a las reivindicaciones 15 a 16 en el que la agitación del polvo implica una cama fluidificada.
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18. El método según las reivindicaciones 15 a 16, en el que la agitación del polvo implica el uso del equipo Resonance Acoustic Mixer (Mezclador Acústico de Resonancia).
- 19 El método conforme a las reivindicaciones 1 a 18 en el que el gas de molienda tiene una humedad
- 25 preferentemente inferior al 15% de humedad relativa, preferiblemente inferior al 10% de humedad relativa, preferiblemente inferior al 5% de humedad relativa, más preferiblemente inferior al 2,5% de humedad relativa.
- 20 El método conforme a las reivindicaciones 1 a 19 en el que el gas de molienda es preferiblemente aire, nitrógeno o helio, o una combinación de los mismos.
- 30
- 21 El método conforme a las reivindicaciones 1 a 20, en el que la co-tritura en molino de chorro se lleva a cabo a una velocidad de alimentación del polvo media comprendida entre 0,1 y 50 g/min, preferiblemente a una velocidad de alimentación entre 0,5 y 40 g/min, preferiblemente a una velocidad de alimentación entre 1 y
- 35 30 g/min, preferiblemente a una velocidad de alimentación entre 1,5 y 25 g/min, preferiblemente a una velocidad de alimentación entre 0,1 y 20 g/min, preferiblemente a una velocidad de alimentación entre 0,5 y 15 g/min, preferiblemente a una velocidad de alimentación entre 1 y 10 g/min, preferiblemente a una velocidad de alimentación entre 1,5 y 5 g/min.
22. El método conforme a las reivindicaciones 1 a 21, en el que la co-tritura en molino de chorro se lleva a cabo a una presión de entrada de entre 3 y 12 bares, preferiblemente a una presión de entrada de entre 4 y 10 bares, o más preferiblemente a una presión de entrada de entre 5 y 9 bares.
- 5 23. El método conforme a las reivindicaciones 1 a 22, en el que la co-tritura en molino de chorro se lleva a cabo a una presión de molienda de más de 2 bares por debajo de la presión de entrada.
24. El método conforme a la reivindicación 23, en donde la presión de molienda se lleva a cabo entre 1 y 10 bares, preferiblemente a una presión de entre 2 y 8 bares o más
- 10 preferiblemente a una presión de entre 3 y 7 bares.
25. El método conforme a cualquiera de las reivindicaciones precedentes, en el que la formulación comprende además un agonista adrenérgico receptor beta-2, preferiblemente en el que el agonista adrenérgico receptor beta-2 es albuterol (salbutamol), metaproterenol, terbutalina, salmeterol, fenoterol,

- 15 procatenol, preferiblemente, formoterol, carmoterol y sales farmacéuticamente aceptables de las mismas, más preferiblemente en el que el agonista adrenérgico receptor beta-2 es (R) -5-[2-(5,6-dietil-indan-2-ilamino)-1-hidroxi-etil]-8-hidroxi-1H -quinolin-2-ona maleato.
26. El método conforme a cualquiera de las reivindicaciones precedentes, en el que la formulación
- 20 comprende glicopirrolato, indacaterol y mometasona, preferiblemente bromuro de glicopirronio, maleato de indacaterol y furoato de mometasona.
27. Un método de fabricación de una formulación de polvo seco; el método comprende co-triturar en molino de chorro el glicopirrolato no micronizado y el estearato de magnesio con gas para molienda el cual tiene una humedad inferior al 20%
- 25 de humedad relativa para producir partículas compuestas micronizadas, en donde las partículas compuestas micronizadas se someten entonces a una etapa de acondicionamiento que incluye la exposición de las partículas compuestas micronizadas a condiciones húmedas con temperaturas entre los 5 ° C y 88 ° C al menos durante 10 minutos.
- 30 28. Una formulación que comprende partículas co-trituradas en molino de chorro y posteriormente co-condicionadas que comprenden glicopirrolato y estearato de magnesio obtenido o que se puede obtener por medio de un método conforme a cualquier reivindicación precedente, opcionalmente para su uso en el tratamiento de una enfermedad respiratoria, o para su uso en la preparación de un medicamento para el tratamiento de una enfermedad respiratoria.
- 35 29. Una formulación o un método como se reivindica en la reivindicación precedente en el que el glicopirrolato es un racemato.
30. Una formulación o un método como se reivindica en la reivindicación precedente en el que el glicopirrolato es un único enantiómero.
31. Una formulación o un método como se reivindica en la reivindicación precedente, en el que el estearato
- 5 de magnesio forma un recubrimiento sobre la superficie de las partículas de glicopirrolato según se mide por medio de la espectroscopia de rayos-X por dispersión de energía.
32. Una formulación o un método conforme a cualquiera de las reivindicaciones precedentes para su uso en una condición respiratoria.
- 10 33. Una formulación conforme a las reivindicaciones 28 a32, que comprende además partículas portadoras, en el que el intervalo del glicopirrolato co-triturado en molino de chorro y co-acondicionado y las partículas de estearato de magnesio es menor que 150, más preferiblemente menor que 125, más preferiblemente menor que 100 o más preferiblemente menos de 50 antes de mezclar con las partículas portadoras.
- 15 34. Un inhalador de polvo seco que contiene una formulación que comprende partículas co-trituradas en molino de chorro y posteriormente co-condicionadas que comprenden glicopirrolato y estearato de magnesio como se reivindica en cualquiera de las reivindicaciones 28 a 33.

- 20 35. Utilización de partículas co-trituradas en molino de chorro y co-condicionadas conforme a cualquiera de las reivindicaciones 28-34 para el tratamiento de una enfermedad respiratoria, preferiblemente en la que la enfermedad respiratoria es una enfermedad pulmonar obstructiva crónica (COPD), asma, fibrosis quística (FC) y enfermedades de las vías respiratorias relacionadas.
- 25 36. Un kit farmacéutico que comprende partículas compuestas micronizadas fabricadas por un método conforme a las reivindicaciones 1-24 y un activo adicional conforme a la reivindicación 25, en formas de dosificación unitarias combinadas o separadas, siendo dichas formas adecuadas para la administración del glicopirrolato co-triturado en molino de chorro y del activo adicional en cantidades efectivas , opcionalmente junto con uno o más dispositivos de inhalación para la administración de ambos activos.

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