ensifentrine substance containing a biuret impurity which could not readily be removed. WO 2018/020249 A1 discusses several possible reagents which may be used to add a urea group in the final step of the production of ensifentrine, but no detailed discussion of the conditions of the final ureation step is provided.

It is desirable to develop a synthetic process for the production of ensifentrine which produces a drug substance with a favourable impurity profile without the need for extensive purification and recrystallisation, and in particular where the drug substance comprises low levels of a biuret impurity.

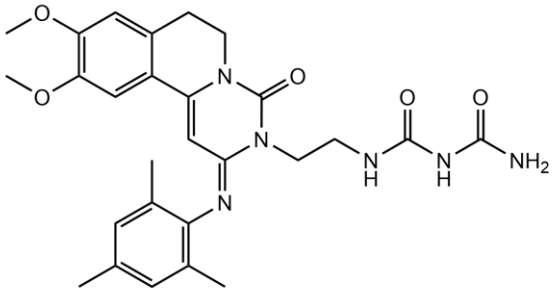
SUMMARY

It has been found that it is possible to produce ensifentrine with a favourable impurity profile, and in particular ensifentrine having low levels of a biuret impurity, by a reaction comprising reacting an amine intermediate with 4-nitrophenyl chloroformate and ammonia in a solvent comprising dichloromethane.

In an aspect, there is provided a particulate composition comprising ensifentrine, wherein the particulate composition further comprises:

from greater than 0.00 wt% to 0.60 wt% of 1,3-bis(2-(2-(mesitylimino)-9,10-dimethoxy-4-oxo-6,7-dihydro-2H-pyrimido[6,1-a]isoquinolin-3(4H)-yl)ethyl)urea (BMIQU) relative to the total weight of ensifentrine; and

from 0.00 wt% to 0.50 wt% of a biuret impurity of formula (A) relative to the total weight of ensifentrine:



(A).

In another aspect, there is also provided a liquid pharmaceutical composition suitable for administration by inhalation comprising (a) the particulate composition as defined above and (b) a diluent.

In another aspect, there is provided a use of the particulate composition as defined above or the liquid pharmaceutical composition as defined above in the manufacture of a medicament for:

a) treating moderate chronic obstructive pulmonary disease (COPD),

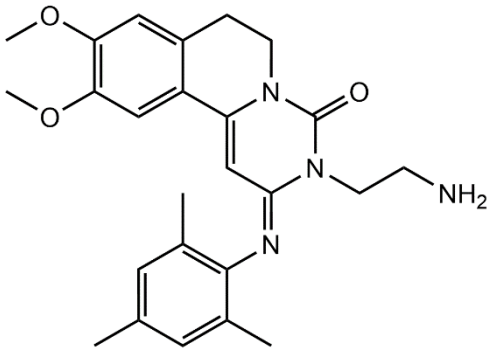
b) treating severe COPD,

c) increasing trough lung function, or

d) reducing frequency of an exacerbation of COPD;

in a human subject in need thereof, wherein the particulate composition or the liquid pharmaceutical composition is to be administered to the human subject via inhalation.

In another aspect, there is provided a process for producing a particulate composition as defined above, the process comprising: reacting a compound of formula (IV) with 4-nitrophenyl chloroformate and ammonia, wherein the compound of formula (IV), 4-nitrophenyl chloroformate and ammonia are reacted in a solvent comprising dichloromethane,



(IV).

Further provided herein, in some examples, are liquid pharmaceutical compositions, wherein the liquid pharmaceutical composition is a suspension comprising, relative to the total weight of the liquid pharmaceutical composition: (a) 1.2 mg/mL ensifentrine; (b) 0.5 mg/ml polysorbate 20; (c) 0.05 mg/ml sorbitan monolaurate; (d) 0.744 mg/ml sodium dihydrogen phosphate; (e) 0.853 mg/ml disodium hydrogen phosphate; (f) 8.6 mg/ml sodium chloride; and (g) water.

Further provided herein, in some examples, is a method of (a) treating moderate chronic obstructive pulmonary disease (COPD); (b) treating severe COPD; (c) increasing trough lung function; or (d) reducing frequency of an exacerbation of

COPD; in a human subject in need thereof, the method comprising administering to the human subject via inhalation the particulate composition or liquid pharmaceutical composition provided herein.

In another aspect, there is provided a kit comprising the particulate composition as defined above or the liquid pharmaceutical composition as defined above.

DETAILED DESCRIPTION OF THE INVENTION

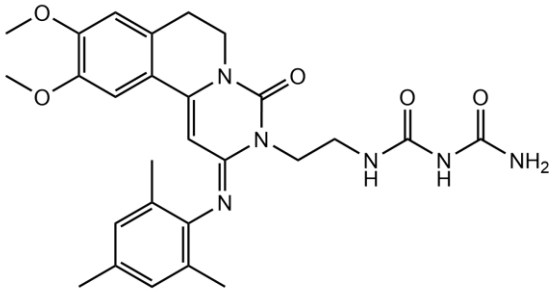
Particulate Composition

CLAIMS

1. A particulate composition comprising ensifentrine, wherein the particulate composition further comprises:

from greater than 0.00 wt% to 0.60 wt% of 1,3-bis(2-(2-(mesitylimino)-9,10-dimethoxy-4-oxo-6,7-dihydro-2H-pyrimido[6,1-a]isoquinolin-3(4H)-yl)ethyl)urea (BMIQU) relative to the total weight of ensifentrine; and

from 0.00 wt% to 0.50 wt% of a biuret impurity of formula (A) relative to the total weight of ensifentrine:



(A).

2. A particulate composition according to claim 1, wherein the particulate composition comprises from 0.00 wt% to 0.30 wt% of the biuret impurity relative to the total weight of ensifentrine.

3. A particulate composition according to claim 1 or claim 2, wherein the particulate composition comprises from 0.00 wt% to 0.05 wt% of the biuret impurity relative to the total weight of ensifentrine.

4. A particulate composition according to any one of the preceding claims, wherein the particulate composition comprises from 0.01 wt% to 0.30 wt% of BMIQU relative to the total weight of ensifentrine.

5. A particulate composition according to any one of the preceding claims, wherein the particulate composition comprises from 0.02 wt% to 0.06 wt% of BMIQU relative to the total weight of ensifentrine.

6. A particulate composition according to any one of the preceding claims, wherein the particulate composition further comprises:

from greater than 0.00 wt% to 0.10 wt% of 1-(2-(9-hydroxy-2-(mesitylimino)-10-methoxy-4-oxo-6,7-dihydro-2H-pyrimido[6,1-a]isoquinolin-3(4H)-yl)ethyl)urea (9-des-methyl impurity); and/or

from greater than 0.00 wt% to 0.10 wt% of 1-(2-(10-hydroxy-2-(mesitylimino)-9-methoxy-4-oxo-6,7-dihydro-2H-pyrimido[6,1-a]isoquinolin-3(4H)-yl)ethyl)urea (10-des-methyl impurity).

7. A particulate composition according to any one of the preceding claims, wherein the particulate composition comprises at least 98.0 wt% of ensifentrine relative to the total weight of the particulate composition.

8. A particulate composition according to any one of the preceding claims, wherein the particulate composition comprises at least 99.0 wt% of ensifentrine relative to the total weight of the particulate composition, optionally at least 99.2 wt% of ensifentrine relative to the total weight of the particulate composition.

9. A particulate composition according to any one of the preceding claims, wherein the particulate composition comprises:

from 99.4 to 99.9 wt% of ensifentrine;

from 0.01 wt% to 0.30 wt% of BMIQU;

from 0.00 wt% to 0.10 wt% of the biuret impurity;

from 0.01 wt% to 0.20 wt% of the 9-des-methyl impurity; and

from 0.01 wt% to 0.20 wt% of the 10-des-methyl impurity,

wherein the wt% is relative to the total weight of the particulate composition.

10. A particulate composition according to any one of the preceding claims, wherein the particulate composition comprises:

from 99.5 to 99.9 wt% of ensifentrine;

from 0.02 wt% to 0.10 wt% of BMIQU;

from 0.00 wt% to 0.04 wt% of the biuret impurity;

from 0.01 wt% to 0.10 wt% of the 9-des-methyl impurity; and

from 0.01 wt% to 0.10 wt% of the 10-des-methyl impurity,

wherein the wt% is relative to the total weight of the particulate composition.

11. A particulate composition according to any one of the preceding claims, wherein the particulate composition consists of:

from 99.6 to 99.9 wt% of ensifentrine;

from 0.02 wt% to 0.10 wt% of BMIQU;

from 0.00 wt% to 0.04 wt% of the biuret impurity;

from 0.01 wt% to 0.10 wt% of the 9-des-methyl impurity;

from 0.01 wt% to 0.10 wt% of the 10-des-methyl impurity; and

no greater than 0.36 wt% total of other related substances,

wherein the wt% is relative to the total weight of the particulate composition.

12. A particulate composition according to any one of the preceding claims, wherein the particulate composition has a Dv50 of from about 0.2 to about 5.0 μm.

13. A particulate composition according to claim 12, wherein the particulate composition has a Dv50 of from about 1.0 μm to about 2.2 μm.

14. A particulate composition according to any one of the preceding claims, wherein the particulate composition has a Dv10 of from about 0.3 μm to about 0.9 μm and/or a Dv90 of from about 2.3 μm to about 4.5 μm.

15. A liquid pharmaceutical composition suitable for administration by inhalation comprising (a) the particulate composition as defined in any one of the preceding claims and (b) a diluent.

16. A liquid pharmaceutical according to claim 15, wherein the particulate composition is suspended in the diluent.

17. A liquid pharmaceutical composition according to claim 15 or claim 16, wherein the liquid pharmaceutical composition comprises no more than 1.00 wt % of BMIQU relative to the total weight of ensifentrine.

18. A liquid pharmaceutical composition according to claim 17, wherein the liquid pharmaceutical composition comprises no more than 0.50 wt % of BMIQU relative to the total weight of ensifentrine.

19. A liquid pharmaceutical composition according to any one of claims 15 to 18, wherein the liquid pharmaceutical composition comprises, relative to the total weight of the liquid pharmaceutical composition:

a) the particulate composition at a concentration of from 0.8 to 1.6 mg/mL;
b) one or more surfactants at a total concentration of from 0.1 to 1.0 mg/mL;
c) one or more buffers at a total concentration of from 1.0 to 2.0 mg/ml; and
d) water.

20. The liquid pharmaceutical composition according to any one of claims 15 to 19, wherein the liquid pharmaceutical composition comprises, relative to the total weight of the liquid pharmaceutical composition:

a) the particulate composition at a concentration of from 1.0 to 1.4 mg/mL;
b) polysorbate 20 (Tween 20) at a concentration of 0.3 to 0.7 mg/mL;
c) sorbitan monolaurate (Span 20) at a concentration of 0.0 to 0.1 mg/mL;
d) sodium dihydrogen phosphate dihydrate at a concentration of 0.5 to 1.0 mg/mL;
e) disodium hydrogen phosphate dihydrate at a concentration of 0.5 to 1.0 mg/mL;
f) sodium chloride at a concentration of 5 to 10 mg/mL; and
g) water.

21. A liquid pharmaceutical composition according to any one of claims 15 to 20, wherein the liquid pharmaceutical composition comprises from about 2.0 mg to about 4.0 mg of the particulate composition.

22. The liquid pharmaceutical composition according to any one of claims 15 to 21, wherein the liquid pharmaceutical composition is a suspension comprising, relative to the total weight of the liquid pharmaceutical composition:

a) 1.2 mg/mL ensifentrine;
b) 0.5 mg/ml polysorbate 20;
c) 0.05 mg/ml sorbitan monolaurate;
d) 0.744 mg/ml sodium dihydrogen phosphate;
e) 0.853 mg/ml disodium hydrogen phosphate;

f) 8.6 mg/ml sodium chloride; and

g) water.

23. Use of the particulate composition of any one of claims 1-14 or the liquid pharmaceutical composition of any one of claims 15-22 in the manufacture of a medicament for:

a) treating moderate chronic obstructive pulmonary disease (COPD),

b) treating severe COPD,

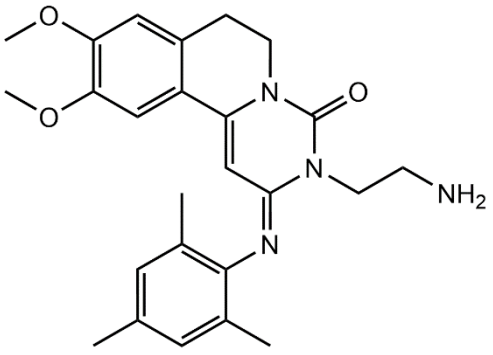
c) increasing trough lung function, or

d) reducing frequency of an exacerbation of COPD;

in a human subject in need thereof, wherein the particulate composition or the liquid pharmaceutical composition is to be administered to the human subject via inhalation.

24. A process for producing a particulate composition as defined in any one of claims 1 to 14, the process comprising:

reacting a compound of formula (IV) with 4-nitrophenyl chloroformate and ammonia, wherein the compound of formula (IV), 4-nitrophenyl chloroformate and ammonia are reacted in a solvent comprising dichloromethane,



(IV).

25. A process according to claim 24, wherein 1 eqv of the compound of formula (IV) is reacted with from 0.8 to 1.5 eqvs of 4-nitrophenyl chloroformate, optionally with from 1.0 to 1.2 eqvs of 4-nitrophenyl chloroformate.

26. A process according to claim 24 or claim 25, wherein the process comprises:

(i) combining the compound of formula (IV) with dichloromethane in a reactor;

(ii) adding an aqueous solution of a base to the reactor;

(iii) adding a solution of 4-nitrophenyl chloroformate in dichloromethane to the reactor; and

(iv) adding a solution of ammonia to the reactor.

27. A process according to claim 26, wherein the base in step (ii) is potassium bicarbonate.

28. A kit comprising the particulate composition of any one of claims 1-14 or the liquid pharmaceutical composition of any one of claims 15- 22.