The dispersible composition (e.g. tablet) of the invention will now be described in more details. Clearly, it has intrinsic properties that allow for the dispersibility (or disintegration) properties.

Hence the disclosure provides a dispersible composition (e.g. tablet) comprising bedaquiline fumarate as the active ingredient and wherein the tablet comprises an intra-granular and extra-granular layer in which the intra-granular layer comprises a non-soluble excipient/diluent and is charaterised in that the intra-granular layer is absent a soluble excipient/diluent that is starch (and in the most preferred embodiment the intra-granular layer is absent any soluble excipient/diluent). In an aspect of the disclosure, there is provided a dispersible composition comprising bedaquiline fumarate as the active ingredient and wherein the composition comprises an intra-granular and extra-granular layer in which the intra-granular layer comprises a non-soluble excipient/diluent and is charaterised in that the intra-granular layer is absent of a soluble excipient/diluent that is starch. For example the intra-granular layer may comprise mannitol as an excipient/diluent (which is classed as a soluble excipient/diluent) but may not contain starch. In the preferred embodiment, the intra-granular layer is absent mannitol and starch (and also absent any other soluble excipient/diluent).

In an embodiment of the disclosure, the intra-granular layer comprises a non-soluble excipient/diluent that is microcrystalline cellulose, but such layer in not necessarily absent a soluble excipient/diluent. Hence, in an aspect, there is provided a dispersible composition comprising bedaquiline fumarate as the active ingredient and wherein the composition comprises an intra-granular and extra-granular layer in which the intra-granular layer comprises a non-soluble excipient/diluent that is microcrystalline cellulose.

In an embodiment, when a soluble excipient/diluent is employed, then it is preferably not starch. This is because starch may swell in water (e.g. by about 5-10%) at 37°C (it may become soluble in hot water at temperatures above the gelatinization temperature.

It is preferred that the intra-granular layer comprises a non-soluble excipient/diluent that is microcrystalline cellulose and that layer is also absent any soluble excipient/diluent.

By "absent", in the context of soluble excipient/diluent, we mean that the composition (e.g. tablet composition) contains an insignificant amount of such ingredient (e.g. in this case soluble excipient/diluent), by which we mean less than 5 % by weight based on the total weight of the composition, more preferably, less than 2.5% by weight, e.g. less than 1%. Most preferably, this means that the ingredient is completely absent, i.e. that there is 0% or near 0% of that ingredient (by weight) – that is a negligible amount of it.

Often, dispersible tablets are manufactured with soluble excipients/diluents, for example sugar-based excipients such as xylitol, fructose, lactose, and the like. However, in this case it was found that soluble excipients were disadvantageous to the dispersibility/disintegrating properties (as indicated in a reference example hereinafter), for example, due to the fact that they may take up water and form a saturated layer preventing further diffusion of solute from the saturated stagnant layer (as per Noyes Whitney's diffusion layer theory) – this phenomenon may be the cause of the adverse impact on the desired dispersion time. It may also be that the soluble excipients are more prone to absorbing environmental moisture. This may also occur if soluble excipients are used in combination with with partly soluble, or insoluble, excipient. In any event, it was clear that the use of a non-soluble excipient, in particular microcryalline cellulose, especially within the intra-granular part of the tablet formulation was key in obtaining a dispersible tablet with the desired properties.

Hence, the disclosure provides a dispersible composition (e.g. tablet composition) comprising (e.g. consisting of) by weight based on the total weight of the composition:
5 to 50% (e.g. 10 to 30%) of active ingredient
35% to 90% (e.g. 50 to 70%) of a non-soluble excipient/diluent
2% to 10% (e.g. 4 to 8%) of a disintegrant
0.1 to 5% (e.g. 1.5 to 3.5%) of a glidant
0.01 to 5% (e.g. 0.1 to 1%) of a wetting agent or surfactant
0 to 10% (e.g. 2 to 5%) of a binder or polymer
0 to 5% (e.g. 1 to 3%) of a lubricant
solvent (qs) e.g. water

which may also be referred to as a composition of the disclosure.

In another aspect of the disclosure there is provided a dispersible composition comprising by weight based on the total weight of the composition:

5 to 50% of active ingredient

35% to 90% of a non-soluble excipient/diluent

2% to 10% of a disintegrant

0.1 to 5% of a glidant

0.01 to 5% of a wetting agent or surfactant

0 to 10% of a binder or polymer

0 to 5% of a lubricant

solvent (qs).

In the case of the above composition, where the non-soluble excipient is microcrystalline cellulose (such as silicified microcrystalline cellulose), then the quantity by weight may be between 20% to 90%, with the remaining amounts of the composition as defined herein. Hence, in an aspect, there is provided a dispersible composition comprising by weight based on the total weight of the composition:
5 to 50% of active ingredient
20% to 90% of a non-soluble excipient/diluent that is microcrystalline cellulose
2% to 10% of a disintegrant
0.1 to 5% of a glidant
0.01 to 5% of a wetting agent or surfactant
0 to 10% of a binder or polymer
0 to 5% of a lubricant
solvent (qs).

The compositions of the disclosure mentioned herein may be charactersied in that they are absent a soluble excipient/diluent.

For instance, most preferably the composition (e.g. tablet composition) consists of by weight, based on the total weight of the composition:
24.18% (or about 25%) of active ingredient
62.12% (or about 60%) non-soluble excipient/diluent (e.g. microcrystalline cellulose, such as silicified microcrystalline cellulose)
6% (or about 6%) disintegrant (e.g. crospovidone, such as Polyplasdone XL)
2.5 % (or about 2.5%) glidant (e.g. colloidal silicon dioxide, Aerosil 200)
0.2% (or about 0.2%) wetting agent or surfactant (e.g. polysorbate 20, i.e. Tween 20)
3% (or about 3%) binder or polymer (e.g. hypromellose 5 cps, i.e. Methocel E 5 LV)
2% (or about 2%) lubricant (e.g. sodium stearyl fumarate (Pruv))
Solvent (qs), e.g. water – if necessary (i.e. only the amount needed, if any)

The disclosure provides provided a composition (e.g. tablet composition) wherein the different parts of the composition, specifically the intra-granular and extra-granular fraction and binder portion, comprise (e.g. consist of) the following ingredients by weight based on the total weight of the composition:

Solvent (qs), e.g. water – if necessary (i.e. only the amount needed, if any)
Extra-granular fraction
10 to 50% (e.g. 20 to 40%) of excipient/diluent (preferably a non-soluble excipient/diluent e.g. microcrystalline cellulose, such as silicified microcrystalline cellulose)
1 to 5% (e.g. 2 to 4%) disintegrant (e.g. crospovidone, such as Polyplasdone XL)
0 to 3% (e.g. 0.1 to 1%) glidant (e.g. colloidal silicon dioxide, Aerosil 200)
0 to 5% (e.g. 1 to 3%) lubricant (e.g. sodium stearyl fumarate (Pruv)).

In another aspect of the present disclosure, there is provided a composition wherein the different parts of the composition, specifically the intra-granular and extra-granular fraction and binder portion, comprise the following ingredients by weight based on the total weight of the composition:
Intra-granular fraction
5 to 50% of active ingredient
10 to 50% of non-soluble excipient/diluent
1 to 5% disintegrant
0.1 to 5% glidant
Binder
1 to 10% binder or polymer
0.01 to 5% wetting agent or surfactant
Solvent (qs)
Extra-granular fraction
10 to 50% of excipient/diluent
1 to 5% disintegrant
0 to 3% glidant
0 to 5% lubricant.

The compositions (e.g. tablet compositions) of the disclosure mentioned herein may be charactersied in that specifically the intra-granular layer is absent any soluble excipient/diluent. Hence, the extra-granular fraction need not be absent any soluble excipient/diluent, although, preferably, it is the case that the extra-granular fraction is also absent any soluble excipient/diluent.

For instance, most preferably the composition consists of the following compositions of intra-granular fraction, binder and extra-granular fraction, by weight based on the total weight of the composition:

Intra-granular fraction

24.18% (or about 25%) of active ingredient

29.82% (or about 30%) of non-soluble excipient/diluent (e.g. microcrystalline cellulose, such as silicified microcrystalline cellulose)

3% (or about 3%) disintegrant (e.g. crospovidone, such as Polyplasdone XL)

2 % (or about 2%) glidant (e.g. colloidal silicon dioxide, Aerosil 200)

Binder

3% (or about 3%) binder or polymer (e.g. hypromellose 5 cps, i.e. Methocel E 5 LV)

0.2% (or about 0.2%) wetting agent or surfactant (e.g. polysorbate 20, i.e. Tween 20)

Solvent (qs), e.g. water – if necessary (i.e. only the amount needed, if any)

Extra-granular fraction

32.3% (or about 30%) of excipient/diluent (preferably a non-soluble excipient/diluent e.g. microcrystalline cellulose, such as silicified microcrystalline cellulose)

3% (or about 3%) disintegrant (e.g. crospovidone, such as Polyplasdone XL)

0.5 % (or about 0.5%) glidant (e.g. colloidal silicon dioxide, Aerosil 200)

2% (or about 2%) lubricant (e.g. sodium stearyl fumarate (Pruv)).

As indicated above, the compositions of the disclosure preferably comprise different fractions/portions, an intra-granular fraction, a binder portion and an extra-granular fraction.

Hence, in an aspect, there is provided a process for the preparation of a composition of the disclosure, which comprises:

(a) obtaining an intra-granular fraction using the intra-granular fraction components mentioned herein;

(b) preparing a binder fraction, using the binder fraction components mentioned herein;

(c) obtaining an extra-granular fraction using the extra-granular fraction components mentioned herein,

and using those fractions to prepare a composition of the disclosure.

More specifically, the intra-granular fraction (as defined herein) may be prepared by mixing or blending the relevant components.

Direct compression may be employed but this may have the disadvantage that the blend has poor flow properties and/or there may be sticking on the surface of punches. Hence, direct compression was followed by granulation. Dry granulation may have disadvantages in relation to flow (or compression) properties and the aforementioned sticking/picking phenomenon may also remain. Hence, for compositions of the disclosure, it is preferred that a wet granulation process is employed.

More specifically therefore, the binder fraction/portion, may be prepared by contacting or mixing the relevant ingredients (i.e. the binder or polymer and wetting agent and, if necessary, a vehicle which may be aqueous or non-aqueous, or a combination; the vehicle is preferably water (qs), preferably purified water (qs)), and that binder fraction/portion may undergo a wet-granulation with the intra-granular fraction. Such wet granulation process is preferably a low shear granulation process (or top spray fluid bed granulation) and, in the binder fraction, a low viscosity soluble polymer (preferably viscosity 5 cps or lower) is employed. The obtained granulate may then be dried and sized (or sieved) after which it is mixed or blended with the components of the extra-granular fraction (as defined herein). Such blending also inherently involves lubrication, if the extra-granular layer also includes a lubricant.

Once a composition of the disclosure has been prepared, for example as set out above, including the mixing of the intra-granular, extra-granular and binder fractions, such composition may optionally, and preferably, be converted into tablet forms. In the process of the disclosure , the compositions so prepared are preferably compressed into tablet form, thereby allowing for the preparation of a dispersible tablet of the disclosure . Such a tablet may be of any suitable dose, but each unit may contain between 5 and 200 mg of active ingredient (in this instance, meaning the active substatnce bedaquiline not considering the fumarate salt component). The unit may contain 100 mg of bedaquiline (plus the corresponding weight of the fumarate salt portion) or, if the unit form is for the pediatric population, then it is preferably 20 mg of bedaquiline (corresponding to 24.18 mg of bedaquiline fumarate).

The tabletting process itself is otherwise standard and readily practised by forming a tablet from desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press.

Tablets of the present disclosure may further be film-coated to improve taste, to provide ease of swallowing and an elegant appearance. Many suitable polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropyl methylcellulose HPMC, especially HPMC 2910 5 mPa.s. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers. Besides a film-forming polymer, the film coat may further comprise a plasticizer (e.g. propylene glycol) and optionally a pigment (e.g. titanium dioxide). The film-coating suspension also may contain talc as an anti-adhesive. In immediate release tablets according to the disclosure , the film coat is small and in terms of weight accounts for less than about 3 % (w/w) of the total tablet weight. In an embodiment of the disclosure (e.g. in a preferred embodiment), the tablets of the disclosure are not film-coated.

In an aspect, there is provided a composition obtainable by the process as mentioned herein.

shows activity against active, sensitive, susceptible *Mycobacteria* strains and latent, dormant, persistent *Mycobacteria* strains.

Hence, there is provided compositions (e.g. tablets) according to the disclosure , which are suitable for the treatment of a bacterial infection including a mycobacterial infection, particularly those diseases caused by pathogenic mycobacteria such as *Mycobacterium tuberculosis* (including the latent and drug resistant form thereof), *M. bovis*, *M. leprae, M. avium, M. leprae* and *M. marinum.*

In an aspect, there is provided a composition as mentioned herein for use in the treatment of tuberculosis.

Further, the present disclosure also relates to the use of a composition (e.g. tablet) of the disclosure, the pharmaceutically acceptable salts thereof, the solvates thereof or the *N*-oxide forms thereof, as well as any of the pharmaceutical compositions thereof as described hereinafter for the manufacture of a medicament for the treatment of a bacterial infection including a mycobacterial infection.

Accordingly, the disclosure provides a method of treating a patient suffering from, or at risk of, a bacterial infection, including a mycobacterial infection, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition (e.g. tablet) according to the disclosure.

The compositions of the disclosure may be combined with other therapeutic agents that are known to be useful in the treatment of a bacterial infection as defined herein (and particularly for the treatment of a mycobacterial infection, tuberculosis as defined herein). In an aspect, there is provided a composition as mentioned herein for use in combination with one or more other therapeutic agent(s) useful in the treatment of tuberculosis. In an aspect, there is provided a combination comprising a composition as mentioned herein and one or more other therapeutic agents useful in the treatment of tuberculosis.

Claims

1. A dispersible composition comprising bedaquiline fumarate as the active ingredient and wherein the composition comprises an intra-granular and extra-granular layer in which the intra-granular layer comprises a non-soluble excipient/diluent and is charaterised in that the intra-granular layer is absent of a soluble excipient/diluent that is starch.

2. A dispersible composition as claimed in Claim 1, wherein the intra-granular layer is absent of any soluble excipient/diluent.

3. A dispersible composition as claimed in Claim 1 or Claim 2, wherein the non-soluble excipient/diluent in the intra-granular layer is microcrystalline cellulose.

4. A dispersible composition comprising bedaquiline fumarate as the active ingredient and wherein the composition comprises an intra-granular and extra-granular layer in which the intra-granular layer comprises a non-soluble excipient/diluent that is microcrystalline cellulose.

5. A dispersible composition as claimed in Claim 3, wherein the intra-granular layer is absent of a soluble excipient/diluent.

6. A dispersible composition as claimed in any one of the preceding claims, wherein the dispersible composition is a tablet.

7. A dispersible composition comprising by weight based on the total weight of the composition:
5 to 50% of active ingredient
35% to 90% of a non-soluble excipient/diluent
2% to 10% of a disintegrant
0.1 to 5% of a glidant
0.01 to 5% of a wetting agent or surfactant
0 to 10% of a binder or polymer
0 to 5% of a lubricant
solvent (qs).

8. A dispersible composition as claimed in claim 7, comprising by weight based on the total weight of the composition:
10 to 30% of active ingredient
50 to 70% of a non-soluble excipient/diluent
4 to 8% of a disintegrant
1.5 to 3.5% of a glidant
0.1 to 1% of a wetting agent or surfactant
2 to 5% of a binder or polymer
1 to 3% of a lubricant
solvent (qs).

9. A dispersible composition comprising by weight based on the total weight of the composition:
5 to 50% of active ingredient

20% to 90% of a non-soluble excipient/diluent that is microcrystalline cellulose
2% to 10% of a disintegrant
0.1 to 5% of a glidant
0.01 to 5% of a wetting agent or surfactant
0 to 10% of a binder or polymer
0 to 5% of a lubricant
solvent (qs).

10. A dispersible composition as claimed in claim 9, comprising by weight based on the total weight of the composition:
10 to 30% of active ingredient
50 to 70% of a non-soluble excipient/diluent that is microcrystalline cellulose
4 to 8% of a disintegrant
1.5 to 3.5% of a glidant
0.1 to 1% of a wetting agent or surfactant
2 to 5% of a binder or polymer
1 to 3% of a lubricant
solvent (qs).

11. A composition as claimed in any one of claims 7 to 10, wherein they are further characterised in that they are absent of a soluble excipient/diluent.

12. A composition as claimed in any of the preceding claims, which composition consists of by weight, based on the total weight of the composition:
24.18% of active ingredient
62.12% non-soluble excipient/diluent
6% disintegrant
2.5 % glidant
0.2% wetting agent or surfactant
3% binder or polymer
2% lubricant
Solvent (qs).

13. A composition as claimed in any one of claims 1 to 11, which composition consists of by weight, based on the total weight of the composition:
25% of active ingredient
60% non-soluble excipient/diluent
6% disintegrant
2.5 % glidant
0.2% wetting agent or surfactant
3% binder or polymer
2% lubricant
Solvent (qs).

14. A composition wherein the different parts of the composition, specifically the intra-granular and extra-granular fraction and binder portion, comprise the following ingredients by weight based on the total weight of the composition:
Intra-granular fraction
5 to 50% of active ingredient
10 to 50% of non-soluble excipient/diluent
1 to 5% disintegrant
0.1 to 5% glidant

Binder
1 to 10% binder or polymer
0.01 to 5% wetting agent or surfactant
Solvent (qs)
Extra-granular fraction
10 to 50% of excipient/diluent
1 to 5% disintegrant
0 to 3% glidant
0 to 5% lubricant.

15. A composition as claimed in Claim 14, wherein the intra-granular layer is absent of any soluble excipient/diluent; and/or, optionally, the extra-granular fraction is also absent of any soluble excipient/diluent.

16. A composition as claimed in Claim 14 or Claim 15, which consists of the following compositions of intra-granular fraction, binder and extra-granular fraction, by weight based on the total weight of the composition:
Intra-granular fraction
24.18% of active ingredient
29.82% of non-soluble excipient/diluent
3% disintegrant
2 % glidant
Binder
3% binder or polymer
0.2% wetting agent or surfactant
Solvent (qs)
Extra-granular fraction
32.3% of excipient/diluent
3% disintegrant

0.5 % glidant
2% lubricant.

17. A composition as claimed in Claim 14 or Claim 15, which consists of the following compositions of intra-granular fraction, binder and extra-granular fraction, by weight based on the total weight of the composition:
Intra-granular fraction
25% of active ingredient
30% of non-soluble excipient/diluent
3% disintegrant
2 % glidant
Binder
3% binder or polymer
0.2% wetting agent or surfactant
Solvent (qs)
Extra-granular fraction
30% of excipient/diluent
3% disintegrant
0.5 % glidant
2% lubricant.

18. A composition as claimed in any one of claims 7 to 17, where the composition is a tablet composition.

19. A composition as claimed in any of Claims 7, 8, 9, 10, 12, 13, 14, 16 and 17, wherein:
the non-soluble excipient/diluent is microcrystalline cellulose;
the disintegrant is crospovidone;
the glidant is colloidal silicon dioxide;
the binder or polymer is hypromellose 5 cps;
the wetting agent or surfactant is polysorbate 20;
the solvent (qs) is water;
(other) excipient/diluent (if applicable) is a non-soluble excipient/diluent microcrystalline cellulose;
the disintegrant is crospovidone;
the glidant is colloidal silicon dioxide; and/or
the lubricant is sodium stearyl fumarate.

19. A composition as claimed in any one of the preceding claims for use in the treatment of tuberculosis.

20. A composition as claimed in Claim 19, for use in the pediatric and/or geriatric population.

21. A composition as claimed in any one of claims 1 to 18 for use in combination with one or more other therapeutic agent(s) useful in the treatment of tuberculosis.

22. A combination comprising a composition as claimed in any one of Claims 1 to 18 and one or more other therapeutic agents useful in the treatment of tuberculosis.

23. A process for preparing a composition as claimed in any one of Claims 1 to 18 which comprises:

(a) obtaining an intra-granular fraction using the intra-granular fraction components mentioned in any one of Claim 14 to 17;

(b) preparing a binder fraction, using the binder fraction components mentioned in any one of Claims 14 to 17;

(c) obtaining an extra-granular fraction using the extra-granular fraction components mentioned in any one of Claims 14 to 17,

and using those fractions to prepare a composition.

24. A composition obtainable by the process as defined in Claim 23.