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 in an aspect of the disclosure there is provided 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). 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 alternative aspect 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 (e.g tablet) comprising bedaquiline fumarate as the active ingredient and wherein the composition (e.g tablet) 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.

When microcrystalline cellulose is referred to, it is intended to include silicified microcrystalline cellulose. This non-soluble excipient/diluent in the intra-granular portion of the tablet of the disclosure is key to its intrinsic dispersibility/disintegrating properties.

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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, in an aspect of the disclosure there is provided 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 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 (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

20% to 90% (e.g. 50 to 70%) of a non-soluble excipient/diluent that is microcrystalline cellulose (such as silicified microcrystalline cellulose)

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.

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)

In another aspect, there is 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:

Intra-granular fraction

5 to 50% (e.g. 10 to 30%) of active ingredient

10 to 50% (e.g. 20 to 40%) of 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)

0.1 to 5% (e.g. 0.5 to 4%, such as 1 to 3%) glidant (e.g. colloidal silicon dioxide, Aerosil 200)

Binder

1 to 10% (e.g. 2 to 5%) 3% binder or polymer (e.g. hypromellose 5 cps, i.e. Methocel E 5 LV)

0.01 to 5% (e.g. 0.1 to 1%) 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
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))

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))

The intra-granular fraction (or portion) may comprise up to 75% by weight of the total weight of the composition (e.g. tablet), and preferably comprises between 40 and 70% (e.g. between 50 and 65%) by weight of the composition (or tablet). Most preferably, the intra-granular fraction (or portion) of the composition (e.g. tablet composition) comprises about 60% of the total weight of the composition. The binder fraction (or portion, or element) may comprise up to 20% by weight of the total weight of the composition (e.g. tablet composition), for example from 0.5 to 10% by weight and preferably between 1 and 8% by weight (e.g. about 3% by weight). The extra-granular layer may comprise up to 60% by weight of the total weight of the composition (e.g. tablet), and preferably comprises between 20 and 50% (e.g. between 30 and 45%) by weight of the composition (or tablet). Most preferably, the extra-granular fraction (or portion) of the composition (e.g. tablet composition) comprises about 37.5% of the total weight of the composition.

In the context of the compositions (e.g.tablet compositions) described herein, the composition may be described as comprising an intra-granular and extra-granular fraction and a binder portion (or fraction). Such fractions or portions of the composition are ultimately intermingled with each other. However, it will be appreciated (for example with reference to the process for preparing such compositions) that the distinction of these fractions (or portions) results in distinct properties for the resultant compositions.

The compositions of the disclosure described herein may be a mixture of or blend of the intra-granular and extra-granular fractions (or portions) and binder portion and may also, after being subjected to a suitable compression technique, take on a (unit) dosage form such as a tablet.

In the disclosure described herein, particularly the dispersible compositions described above, the total tablet weight may be about 100 mg (and hence, the active ingredient present may be between 5 to 50 mg, such as between about 10 mg and 30 mg, e.g. about 20 mg). In this manner a pediatric (or geriatric) formulation may be provided in which there is about 20 mg of active ingredient. In the disclosure, particularly those described below, the total tablet weight may be higher (but may still deliver the same quantity of active ingredient), for instance, a dispersible formulation of 200 mg may be provided to also deliver about 20 mg of active ingredient, for instance in the percentages that may be described below.

In the disclosure, there may also be provided dispersible compositions with the following features, which applies in particular to compositions of the disclosure where the total tablet weight is relatively high (for instance greater than 100 mg, e.g. a total tablet weight of 200 mg):

- there is provided 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. 5 to 20% or 10 to 15%) of active ingredient
  35% to 90% (e.g. 60 to 80% or 70 to 75%) 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
- there is provided a dispersible composition (e.g. tablet composition) comprising (e.g. consisting of) by weight based on the total weight of the composition:
  12.09% (or about 12%) of active ingredient
  73.71% (or about 70%) 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)

In the disclosure, in particular to those compositions of the disclosure where the total tablet weight is relatively high (e.g. 200 mg):

- there is 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:

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))

The compositions of the disclosure are described as having certain components or ingredients, which is elaborated below.

By "active ingredient" we mean bedaquiline fumarate, i.e. the fumarate salt form of bedaquiline. This is the form that is a part of the adult composition that has been received regulatory approval in some territories.

It is indicated herein that the compositions (e.g. tablet compositions) of the disclosure contain a non-soluble excipient/diluent. Unless that excipient is already specified, such excipient/diluent may be starch, powdered cellulose, microcrystalline cellulose (such as silicified microcrystalline cellulose), calcium phosphates (e.g. dibasic calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate), calcium carbonate, calcium sulfate or the like (or combinations thereof, i.e. co-processed non-soluble excipients; others that may be considered include wax-like hydrogenated oils and the like). It is understood that the most preferred non-soluble excipient/diluent is microcrystalline cellulose (e.g. silicified microcrystalline cellulose) because this results in compositions with intrinsic properties that are advantageous. Where it is mentioned that the excipient/diluent need not be non-soluble, then sugars and polyols may also be considered, for instance the following excipients/diluents may also be considered: dextrates, dextrin, dextrose excipient, fructose, kaolin, lactitol, lactose anhydrous, lactose monohydrate, mannitol, sorbitol, sodium chloride, sucrose, compressible sugar, confectioner's sugar, a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25), commercially available as Microcelac®, a co-processed spray-dried mixture of microcrystalline cellulose and colloidal silicon

dioxide (98:2), commercially available as Prosolv® (which possibilities include sugars and other soluble excipients/diluents).

It is indicated herein that the compositions (e.g. tablet compositions) of the disclosure contain a disintegrant. Possible disintegrants include pharmaceutically acceptable disintegrants comprising starch, ion exchange resins, e.g. Amberlite, cross-linked polyvinylpyrrolidone, modified cellulose gum, e.g. croscarmellose sodium (e.g. Ac-di-Sol®), sodium starch glycollate, sodium carboxymethylcellulose, sodium dodecyl sulphate, modified corn starch, microcrystalline cellulose, magnesium aluminium silicate, alginic acid, alginate, powdered cellulose, crospovidone (such as Polyplasdone XL). Other disintegrants that may be considered include L-HPC, Xanthan gum, Gellan gum, soy polysaccharides, and the like. The most preferred disintegrant is crospovidone, preferably a coarse grade crospovidone (such as Polyplasdone XL).

It is indicated herein that the compositions (e.g. tablet compositions) of the disclosure contain a glidant. Possible glidants include pharmaceutically acceptable glidants comprising talc, colloidal silicon dioxide, starch, magnesium stearate. Preferred is colloidal silicon dioxide (Aerosil 200)

It is indicated herein that the compositions (e.g. tablet compositions) of the disclosure contain a wetting agent or surfactant. Such wetting agent (or surfactant) may be any of the physiologically tolerable wetting agents suitable for use in a pharmaceutical composition.

It is well-known in the art that a wetting agent is an amphiphilic compound; it contains polar, hydrophilic moieties as well as non-polar, hydrophobic moieties.

The terms "hydrophilic" or "hydrophobic" are relative terms.

The relative hydrophilicity or hydrophobicity of a wetting agent may be expressed by its hydrophilic-lipophilic balance value ("HLB value). Wetting agents with a lower HLB value are catagorized as being "hydrophobic" wetting agents whereas wetting agents with a higher HLB value are catagorized as being "hydrophilic" wetting agents. As a rule of thumb, wetting agents having a HLB value greater than about 10 are

generally considered as being hydrophilic wetting agents; wetting agents having a HLB value lower than about 10 are generally considered as being hydrophobic wetting agents.

The present compositions preferably comprise a hydrophilic wetting agent.

It should be appreciated that the HLB value of a wetting agent is only a rough guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a particular wetting agent may vary depending upon the method used to determine the HLB value; may vary depending on its commercial source; is subject to batch to batch variability. A person skilled in the art can readily identify hydrophilic wetting agents suitable for use in the pharmaceutical compositions of the present disclosure .

The wetting agent of the present disclosure can be an anionic, a cationic, a zwitterionic or a non-ionic wetting agent, the latter being preferred. The wetting agent of the present disclosure can also be a mixture of two or more wetting agents.

Suitable wetting agents for use in the compositions of the present disclosure are listed below. It should be emphasized that said list of wetting agents is only illustrative, representative and not exhaustive. Thus the disclosure is not limited to the wetting agents listed below. In the present compositions, also mixtures of wetting agents may be used.

Suitable wetting agents which may be used in the present disclosure comprise:

a) Polyethylene glycol fatty acid monoesters comprising esters of lauric acid, oleic acid, stearic acid, ricinoic acid and the like with PEG 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 32, 40, 45, 50, 55, 100, 200, 300, 400, 600 and the like, for instance PEG-6 laurate or stearate, PEG-7 oleate or laurate, PEG-8 laurate or oleate or stearate, PEG-9 oleate or stearate, PEG-10 laurate or oleate or stearate, PEG-12 laurate or oleate or stearate or ricinoleate, PEG-15 stearate or oleate, PEG-20 laurate or oleate or stearate, PEG-25 stearate, PEG-32 laurate or oleate or stearate, PEG-30 stearate, PEG-40 laurate or oleate or stearate, PEG-45 stearate, PEG-50 stearate, PEG-55 stearate, PEG-100 oleate or stearate, PEG-200 oleate, PEG-400 oleate, PEG-600 oleate; (the wetting agents belonging to this group are for instance known as Cithrol, Algon, Kessco, Lauridac, Mapeg, Cremophor, Emulgante, Nikkol, Myrj, Crodet,

The preferred quantity of wetting agent (or surfactant) is described herein, but it is appreciated however that when used in the present compositions, it may depend on the amount of active ingredient present in the composition or on the particle size of the active ingredient. A higher amount or a smaller particle size may require more wetting agent.

It is indicated herein that the compositions (e.g. tablet compositions) of the disclosure contain a binder or polymer (for instance for the binder fraction of the compositions of the disclosure ). Such a binder or polymer may be an organic polymer.

The organic polymer used in the compositions (e.g. tablets) of the disclosure may be any of the physiologically tolerable water soluble synthetic, semi-synthetic or non-synthetic organic polymers.

Thus for example the polymer may be a natural polymer such as a polysaccharide or polypeptide or a derivative thereof, or a synthetic polymer such as a polyalkylene oxide (e.g. PEG), polyacrylate, polyvinylpyrrolidone, etc. Mixed polymers, e.g. block copolymers and glycopeptides may of course also be used.

The polymer conveniently has a molecular weight in the range 500D to 2 MD, and conveniently has an apparent viscosity of 1 to 15,000 mPa.s when in a 2% aqueous solution at 20°C. For example, the water-soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyakylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,
- hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose,
- carboxyalkylcelluloses such as carboxymethylcellulose,
- alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose,
- carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,
- carboxyalkylcellulose esters,
- starches,
- pectins such as sodium carboxymethylamylopectin,
- chitin derivates such as chitosan,

- heparin and heparinoids,
- polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gum arabic, guargum and xanthan gum,
- polyacrylic acids and the salts thereof,
- polymethacrylic acids and the salts thereof, methacrylate copolymers,
- polyvinylalcohol,
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate,
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide, e.g. poloxamers and poloxamines.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing compositions according to the present disclosure.

Preferably the organic polymer is starch, polyvinylpyrrolidone or a cellulose ether, e.g. PVP K29-32, PVP K90, methyl cellulose, hydroxypropylcellulose, hydroxyethyl methylcellulose, or hydroxypropyl methylcellulose (HPMC).

Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. A preferred HPMC is hypromellose 2910 15 mPa.s or hypromellose 2910 5mPa.s, especially hypromellose 2910 15 mPa.s. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups; 15 mPa.s or 5 mPa.s is a value indicative of the apparent viscosity of a 2 % aqueous solution at 20°C.

It is most preferred that the binder or polymer of the compositions of the disclosure is hypromellose 5 cps (i.e. Methocel E 5 LV).

It is indicated herein that the compositions (e.g. tablet compositions) of the disclosure contain a lubricant. Such a lubricant may be pharmaceutically acceptable lubricants such as magnesium stearate, calcium stearate, stearic acid, talc, polyethylene glycol, sodium lauryl sulfate, magnesium lauryl sulphate. It is most preferred that the lubricant is sodium stearyl fumarate (Pruv).

The compositions of the disclosure may make use of active ingredient having a particle size of:

- $d^{10}$ less than 50μm (preferably less than 25μm, for instance less than 15μm, e.g. around 9μm (or even less)
- $d^{50}$ less than 100μm (preferably less than 50μm, for instance less than 25μm, e.g. around 22μm (or even less)
- $d^{90}$ less than 200μm (preferably less than 100μm, for instance less than 50μm, e.g. around 48μm (or even less)

As used herein, the term $d^{50}$ has its conventional meaning as known to the person skilled in the art and can be measured by art-known particle size measuring techniques such as, for example, sedimentation field flow fractionation, photon correlation spectroscopy, laser diffraction or disk centrifugation. The $d^{50}$ mentioned herein may be related to volume distributions of the particles. In that instance, by "a $d^{50}$ of 22 μm" it is meant that at least 50% of the volume of the particles has a particle size of less than 22 μm. The same applies to the other particle sizes mentioned and $d^{10}$ and $d^{90}$ have analogous meanings. Usually volume and weight distribution result in the same or about the same value for the average particle size.

The particle size can be an important factor determining the tabletting speed, in particular the flowability and therefore the manufacturability on a large scale of a particular dosage form or formulation, and the quality of the final product. For instance, for capsules, the particle size may range preferably from about 5 to about 300 μm ($d^{50}$); for tablets the particle size is preferably less than 250 μm, more preferably less than 100 μm (e.g. less than 50 μm) ($d^{50}$). Too small particles can cause sticking on the tablet punches and manufacturability issues. The particle size has an effect on the intrinsic properties of the compositions of the disclosure.

The compositions as described herein may further comprise one or more pharmaceutically acceptable excipients such as, for example, plasticizers, flavours, sweeteners, coluorants, preservatives and the like (provided that such additional excipients do not comprise soluble excipients/diluents, where it is already specified that the composition or fraction of that composition, as appropriate, does not comprise such soluble components). In the disclosure, the compositions of the disclosure do not contain a plasticizer or another such optional excipient mentioned here. Especially in case of preparation by hot melt extrusion, said excipients should not be heat-sensitive, in other words, they should not show any appreciable degradation or decomposition at the working temperature of the melt-extruder.

The advantage of the present combinations of the disclosure , and specifically the dispersibility/disintegrating properties, may stem from the presence of the non-soluble excipient (e.g. microcrystalline cellulose, such as silicified microcrystalline cellulose) which may have the ability to rapidly intake water in the dispersion medium, i.e. it may have a wicking action that advantageously results in the improved dispersibility/disintegrating properties. In view of this, advantageously, the compositions of the disclosure achieve a favourable dispersibiltiy or disintegrating action, for example as compared to compositions previously known or as compared to other compositions as may be described herein. As indicated, wicking action may lead to faster dispersion and may by-pass the solubilization process (for instance, liquid may be drawn up or "wicked" into these pathways through capilliary action and rupture the interparticulate bonds, causing the tablet/composition to break apart), which could be advantageous. Further, the non-soluble excipients/diluents may easily be re-suspended even after a long period of time (e.g. 6 hours) – this may have the advantage that the compositions of the disclosure do not require a suspending agent to re-disperse the granules/particles.

The disclosure also relates to process for preparing the compositions of the disclosure (e.g. the tablet compositions) and there is therefore provided:

- A process (e.g. as described hereinbelow) for the preparation of composition (e.g. tablet) of the disclosure
- A product (e.g. composition to the disclosure , e.g. a dispersible tablet as described herein) obtainable by a process of the disclosure (e.g. as described hereinbelow)

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 process 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 a preferred aspect of 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.

As indicated above, the utility of the disclosure arises from the active ingredient, and salt thereof, being known to show activity against *Mycobacteria* including drug resistant strains, in particular *Mycobacterium tuberculosis, M. bovis, M. avium, M. leprae and M. marinum*, especially against *Mycobacterium tuberculosis*, including drug-resistant *M. tuberculosis* strains. The active ingredient, including salt thereof,

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 (e.g. MDR 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.

Such other antibacterial agents comprise antibiotics of the β-lactam group such as natural penicillins, semisynthetic penicillins, natural cephalosporins, semisynthetic cephalosporins, cephamycins, 1-oxacephems, clavulanic acids, penems, carbapenems, nocardicins, monobactams; tetracyclines, anhydrotetracyclines, anthracyclines; aminoglycosides; nucleosides such as *N*-nucleosides, C-nucleosides, carbocyclic nucleosides, blasticidin S; macrolides such as 12-membered ring macrolides, 14-membered ring macrolides, 16-membered ring macrolides; ansamycins; peptides such as bleomycins, gramicidins, polymyxins, bacitracins, large ring peptide antibiotics containing lactone linkages, actinomycins, amphomycin, capreomycin, distamycin, enduracidins, mikamycin, neocarzinostatin, stendomycin, viomycin, virginiamycin; cycloheximide; cycloserine; variotin; sarkomycin A; novobiocin;

griseofulvin; chloramphenicol; mitomycins; fumagillin; monensins; pyrrolnitrin; fosfomycin; fusidic acid; D-(*p*-hydroxyphenyl)glycine; D-phenylglycine; enediynes.

Specific antibiotics which may be combined with the present compositions of the disclosure are for example benzylpenicillin (potassium, procaine, benzathine), phenoxymethylpenicillin (potassium), phenethicillin potassium, propicillin, carbenicillin (disodium, phenyl sodium, indanyl sodium), sulbenicillin, ticarcillin disodium, methicillin sodium, oxacillin sodium, cloxacillin sodium, dicloxacillin, flucloxacillin, ampicillin, mezlocillin, piperacillin sodium, amoxicillin, ciclacillin, hectacillin, sulbactam sodium, talampicillin hydrochloride, bacampicillin hydrochloride, pivmecillinam, cephalexin, cefaclor, cephaloglycin, cefadroxil, cephradine, cefroxadine, cephapirin sodium, cephalothin sodium, cephacetrile sodium, cefsulodin sodium, cephaloridine, cefatrizine, cefoperazone sodium, cefamandole, vefotiam hydrochloride, cefazolin sodium, ceftizoxime sodium, cefotaxime sodium, cefmenoxime hydrochloride, cefuroxime, ceftriaxone sodium, ceftazidime, cefoxitin, cefmetazole, cefotetan, latamoxef, clavulanic acid, imipenem, aztreonam, tetracycline, chlortetracycline hydrochloride, demethylchlortetracycline, oxytetracycline, methacycline, doxycycline, rolitetracycline, minocycline, daunorubicin hydrochloride, doxorubicin, aclarubicin, kanamycin sulfate, bekanamycin, tobramycin, gentamycin sulfate, dibekacin, amikacin, micronomicin, ribostamycin, neomycin sulfate, paromomycin sulfate, streptomycin sulfate, dihydrostreptomycin, destomycin A, hygromycin B, apramycin, sisomicin, netilmicin sulfate, spectinomycin hydrochloride, astromicin sulfate, validamycin, kasugamycin, polyoxin, blasticidin S, erythromycin, erythromycin estolate, oleandomycin phosphate, tracetyloleandomycin, kitasamycin, josamycin, spiramycin, tylosin, ivermectin, midecamycin, bleomycin sulfate, peplomycin sulfate, gramicidin S, polymyxin B, bacitracin, colistin sulfate, colistinmethanesulfonate sodium, enramycin, mikamycin, virginiamycin, capreomycin sulfate, viomycin, enviomycin, vancomycin, actinomycin D, neocarzinostatin, bestatin, pepstatin, monensin, lasalocid, salinomycin, amphotericin B, nystatin, natamycin, trichomycin, mithramycin, lincomycin, clindamycin, clindamycin palmitate hydrochloride, flavophospholipol, cycloserine, pecilocin, griseofulvin, chloramphenicol, chloramphenicol palmitate, mitomycin C, pyrrolnitrin, fosfomycin, fusidic acid, bicozamycin, tiamulin, siccanin.

Other Mycobacterial agents which may be combined with the compositions of the disclosure are for example rifampicin (=rifampin); isoniazid; pyrazinamide; amikacin; ethionamide; ethambutol; streptomycin; para-aminosalicylic acid; cycloserine; capreomycin; kanamycin; thioacetazone; PA-824; quinolones/fluoroquinolones such as for example moxifloxacin, gatifloxacin, ofloxacin, ciprofloxacin, sparfloxacin; macrolides such as for example clarithromycin, clofazimine, amoxycillin with clavulanic acid; rifamycins; rifabutin; rifapentine.

The term "about" as used herein in connection with a numerical value is meant to have its usual meaning in the context of the numerical value. Where necessary the word "about" may be replaced by the numerical value ±10%, or ±5%, or ±2%, or ±1%. All documents cited herein are incorporated by reference in their entirety.

The following examples are intended to illustrate the present disclosure.

Experimental part

The active ingredient, bedaquiline fumarate, may be prepared for example in accordance with the procedures described in international patent application WO 2008/068231. As seen from Table 1 below, TMC207 refers to Bedaquiline Fumarate.