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(54) **Title**: DRY POWDER FORMULATIONS COMPRISING TIOTROPIUM, FORMOTEROL AND BUDESONIDE

(57) **Abstract**: The present invention relates to pharmaceutical formulations in dry powder form comprising tiotropium, formoterol and budesonide in order to be used in respiratory tract diseases.

DRY POWDER FORMULATIONS COMPRISING TIOTROPIUM, FORMOTEROL AND BUDESONIDE

The present invention relates to pharmaceutical formulations in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof in order to be used in symptomatic and/or prophylactic treatment of respiratory tract diseases, particularly asthma and COPD.

In case of respiratory tract diseases such as asthma or chronic obstructive pulmonary disease (COPD); stimulants such as allergen, infection, good and bad smell, smoke cause constricted muscles covering the airways, in other words bronchoconstriction, excessive secretion in glands and consequently contraction in the airways. In this case, the patient cannot exhale the inhaled air or he/she cannot inhale.

β2-adrenergic agonists used in the treatment of respiratory tract diseases such as asthma and COPD activate β2-adrenergic receptors and affect the muscles around the airways; alleviate or remove bronchospasm. β2-adrenergic agonists –which are bronchodilators- divide into two groups as short-acting and long-acting. Since short-acting β2 agonists have short onset of time, they are given as relaxant. However, they should be administered frequently as their effect last short. Salbutamol, levosalbutamol, procaterol, fenoterol, terbutaline, pirbuterol, metaproterenol ve bitolterol mesylate can be listed among short-acting β2 agonists. Long-acting β2 agonists can be used more frequently in the treatment of patients suffering symptoms of asthma at nights and exercise-induced asthma. Formoterol, salmeterol, bambuterol and clenbuterol are examples of long-acting β2 agonists.

Corticostereoids, which is another group of active agents used in the treatment of asthma and COPD, are synthetic and potent anti-inflammatory drugs similar to natural corticosteroid hormones secreted by adrenal glands. It is known that corticosteroids are quite effective drugs in asthma treatment. Budesonide, beclomethasone, flunisolide and fluticasone are among molecules belonging to this group.

Another group of active agents used in the treatment of respiratory tract diseases is anticholinergics. Anticholinergics affect the muscles on bronchi including large airways. Like β2-adrenergic agonists, these drugs divide into two as short-acting and long-acting too. Short-acting anticholinergics are generally used to alleviate symptoms while long-acting anticholinergics are used to prevent inhalation problems. Ipratropium bromide and oxitropium

bromide can be listed among short-acting anticholinergics. Tiotropium is a long-acting anticholinergic agent. Tiotropium starts to act in 20 minutes following its intake and its effects can be observed in 24 hours thus it suffices to take tiotropium once a day.

Use of combination drugs in the treatment of respiratory tract diseases such as asthma and COPD is quite effective, particularly in reducing the number of asthma attacks. Since activity of the active agents used in combination drugs can be enabled in smaller doses compared to their use alone, severity of potential side effects and/or their possibility of occurrence can decrease.

The fact that the dry powder formulation comprising active agent combination has good flow characteristics is an important criterion in terms of inhalation of said formulation effectively and therefore in terms of providing an effective treatment. In the case that a dry powder formulation which does not have good flow characteristics is obtained, it is seen that the formulation has low homogeneity and consequently dosing accuracy cannot be ensured during filling the dry powder formulation prepared into reservoirs of multi dose inhalators comprising more than one dose or into blister cavities of a blister package, each of them comprising one dose, or into capsules comprising one dose. Furthermore, the fact that the dry powder formulation does not have good flow characteristics affects emptying capacity and emptying attribute negatively during inhalation of the formulation from capsule, blister or reservoir. As a result, due to the reasons listed above, the active agents cannot reach to the lungs in sufficient amounts.

In order to ease the delivery of the active agents having therapeutic effect in quite small doses by the inhalation route, the active agents are diluted by various non-functional excipients. The physical characteristics of these excipients, used in quite high amounts as compared to the active agent amount in the formulations, such as average particle size have an important role in providing good flow in the dry powder formulation. Since the active agents used are delivered to the lungs in sufficient amounts and in a controlled manner in the dry powder formulation having good flow characteristics, desired therapeutic effect is obtained.

The inventors have developed dry powder formulations which comprise tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof and have high homogeneity and good flow characteristics wherein dosing accuracy is ensured and sufficient amount of active agent can be delivered to the lungs.

Description of the Invention

The present invention relates to pharmaceutical formulations in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof.

Surprisingly, the inventors have seen that dry powder formulations which comprise tiotropium, formoterol and budesonide having a ratio in the range of 0,5: 0.05:3 to 1:3:45, preferably in the range of 1:0.1:2 to 1:2:40 to each other by weight and also at least one pharmaceutically acceptable fine grained and coarse grained excipient having an average particle size ratio to each other in the range of 1:30 to 1:2, preferably in the range of 1:20 to 1:5, more preferably in the range of 1:15 to 1:10 have good flow characteristics and high homogeneous dispersion, therefore dose accuracy is obtained in the formulations and sufficient amount of active agent can be delivered to the lungs.

The fine grained excipient used in the text refers to an excipient having an average particle size less than 10 μm, preferably in the range of 0.1 to 9.9 μm, more preferably in the range of 2 to 8 μm, for instance in the range of 0.3, 0.5, 0.7, 0.9, 1.1, 1.3, 1.5, 1.7, 1.9, 2.3, 2.5, 3.0, 3.5, 4.0, 4.5 to 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5 μm; the coarse grained excipient used in the text refers to an excipient having an average particle size in the range of 10 to 90 μm, preferably in the range of 12 to 85 μm, more preferably in the range of 15 to 80 μm, for instance in the range of 15, 20, 25, 30, 35, 40, 45 to 50, 55, 60, 65, 70, 75, 80, 85 μm.

According to this, the subject of the present invention is the pharmaceutical formulation in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that

- the ratio of tiotropium, formoterol and budesonide to each other respectively is in the range of 0,5: 0.05:3 to 1:3:45, preferably in the range of 1:0.1:2 to 1:2:40 by weight,
- the excipient comprised in said formulation is composed of at least one pharmaceutically acceptable excipient mixture comprising fine grained excipient and coarse grained excipient and
- the average particle size ratio of the fine grained excipient to the coarse grained excipient is in the range of 1:30 to 1:2, preferably in the range of 1:20 to 1:5, more preferably in the range of 1:15 to 1:10.

According to the present invention, tiotropium and/or pharmaceutically acceptable derivatives thereof which is one of the active agents comprised in the dry powder drug formulation

comprising the active agent combination refers to tiotropium's free base, pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof.

According to the present invention, formoterol and/or pharmaceutically acceptable derivatives thereof which is one of the active agents comprised in the dry powder drug formulation comprising the active agent combination refers to formoterol's free base, pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or a combination thereof. Preferably, formoterol fumarate is used.

According to the present invention, budesonide and/or pharmaceutically acceptable derivatives thereof which is one of the active agents comprised in the dry powder drug formulation comprising the active agent combination refers to budesonide's free base, pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or combinations thereof.

According to the present invention, the inhalation formulation comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof can be delivered to the patient in dry powder form. Said dry powder formulations further comprise at least one physiologically and pharmaceutically acceptable excipient along with the active agent. This excipient is composed of fine grained excipient, coarse grained excipient or a combination thereof, preferably a combination of fine grained excipient and coarse grained excipient. This excipient can be selected from monosaccharides (glucose etc.), disaccharides (lactose, saccharose, maltose or pharmaceutically acceptable hydrates, anhydrates or a combination thereof etc.), oligosaccharides and polysaccharides (dextrant etc.), polyalcohols (sorbitol, mannitol, xylitol etc.), salts (sodium chloride, calcium carbonate etc.) or a combination thereof. Same or different substances are used as fine grained excipient and coarse grained excipient, though preferably the same substance is used. Fine grained and coarse grained excipients are preferably lactose, more preferably lactose anhydrate. According to the present invention, the amount of the pharmaceutically acceptable excipient is preferably in the range of 1-50 mg, preferably in the range of 2-40 mg, more preferably in the range of 3-30 mg.

On the other hand, along with the particle size of the excipient comprised in the dry powder formulations of the present invention, the average particle size of the active agent used is quite important in order that the formulation to be obtained has good flow characteristics and therefore an effective inhalation is performed.

The inventors have seen that use of active agents having an average particle size in the range of 1 μm to 10 μm, preferably in the range of 1.5 μm to 7.5 μm, more preferably in the range of 1.5 μm to 5 μm has a significant contribution to the formulation obtained for having proper flow characteristics and for having dose uniformity and to delivery of the active agent to the lungs in sufficient amount.

According to this, the subject of the present invention is pharmaceutical formulations in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that

- the ratio of tiotropium, formoterol and budesonide to each other respectively is in the range of 0,5: 0.05:3 to 1:3:45, preferably in the range of 1:0.1:2 to 1:2:40 by weight,
- the average particle size ratio of fine grained excipient: coarse grained excipient is in the range of 1:30 to 1:2, preferably in the range of 1:20 to 1:5, more preferably in the range of 1:15 to 1:10 and
- the average particle size of the active agents used is in the range of 1 μm to 10 μm, preferably in the range of 1.5 μm to 7.5 μm, more preferably in the range of 1.5 μm to 5 μm.

The amounts of said fine grained and coarse grained excipients constituting the excipient combination having two different average particle sizes as fine grained and coarse grained comprised in the dry powder formulation of the present invention is an important criterion in obtaining the characteristics that can provide an effective treatment. The inventors have seen that characteristics such as proper flow, particularly homogenous particle dispersion and dose uniformity of the formulation are ensured and therefore the sufficient amount of the active agent reaches to the lungs more easily in the case that the ratio of fine grained excipient to coarse grained excipient constituting the excipient combination is in the range of 1:1 to 1:25 by weight, preferably in the range of 1:1 to 1:10 by weight, more preferably in the range of 1:1.5 to 1:5 by weight.

In another aspect, the subject of the present invention is the pharmaceutical formulations in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that

- the ratio of tiotropium, formoterol and budesonide to each other respectively is in the range of 0,5: 0.05:3 to 1:3:45, preferably in the range of 1:0.1:2 to 1:2:40 by weight,
- the average particle size ratio of fine grained excipient: coarse grained excipient is in the range of 1:30 to 1:2, preferably in the range of 1:20 to 1:5, more preferably in the range of 1:15 to 1:10 and
- the ratio of fine grained excipient to coarse grained excipient is in the range of 1:1 to 1:25 by weight, preferably in the range of 1:1 to 1:10 by weight, more preferably in the range of 1:1.5 to 1:5 by weight.

The process for preparation of the pharmaceutical formulations of the present invention in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof is composed of the following steps:

I. micronizing tiotropium, formoterol and budesonide so as to bring them to the desired particle size,
II. micronizing the excipient so as to bring it to the desired particle size,
III. mixing the active agents micronized in the Ist step firstly with the fine grained excipient and then the coarse grained excipient in a mixer or firstly with the coarse grained excipient and then the fine grained excipient in a mixer and
IV. consequently, filling the mixture obtained in dry powder form into appropriate capsules, blisters or reservoirs and making it ready for use.

In another aspect, the present invention relates to inhalation of the dry powder formulations comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof by using inhalation devices comprising capsule, blister or reservoir.

In the case that the dry powder formulation of the present invention is inhaled from capsule, which is one of the inhalation methods, the inventors have found that the inhalation is performed most productively when capsule volume comprising the drug in dry powder form of the present invention comprising tiotropium, formoterol and budesonide and/or

pharmaceutically acceptable derivatives thereof is in the range of 0.1 to 0.5 ml, preferably in the range of 0.15-0.45 ml, more preferably in the range of 0.2-0.4 ml.

According to this, in the case that the dry powder formulation of the present invention is inhaled from capsule, the present invention is characterized in that volume of the capsule used for storage and delivery of the drug in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof is in the range of 0.1 to 0.5 ml, preferably in the range of 0.15-0.45 ml, more preferably in the range of 0.2-0.4 ml.

In another aspect, the inventors have seen that the active agent combination comprised in the capsule is protected from external factors as well as the possibility of moistening that can arise from the nature of the capsule itself is removed in the case that moisture ratio of the package in capsule form having high protection property against moisture and other negative external factors is in the range of 5-20%, preferably in the range of 7-15%. Thus, effective delivery of the formulation in dry powder form of the present invention to the lungs of the patient is enabled by preventing agglomeration.

According to this, in the case that the dry powder formulation of the present invention is inhaled from capsule, the present invention is characterized in that moisture ratio of the package in capsule form used for storage and delivery of the drug in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof is in the range of 5-20%, preferably in the range of 7-15%.

In another aspect, in the case that the dry powder formulation of the present invention is inhaled from capsule, the capsule preferred to be used in the scope of the present invention can be made of a substance selected from a group comprising gelatine, chitosan, starch and/or starch derivatives, cellulose and/or cellulose derivatives or synthetic polymers, and it is composed of telescoping body and cap parts.

According to this, in the case that the dry powder formulation of the present invention is inhaled from capsule, capsule material can be selected from a group comprising hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose if the capsule to be used is made of cellulose and its derivatives. In the case that the dry powder formulation of the present invention is inhaled from capsule, capsule material can be selected from a group comprising polyethylene,

polyester, polyethyleneterephthalate, polycarbonate or polypropylene if the capsule to be used is made of synthetic polymer.

In the case that the dry powder formulation of the present invention is inhaled from capsule, various molecular weighted polyethylene glycol, sorbitol, glycerol, propylene glycol, polyethylene oxide-propylene oxide block copolymers and/or other polyalcohols and polyethers can be added as adjuvant if the capsule material to be used is made of gelatine.

In another aspect, the inventors have found that in the case that fullness ratio of the capsule cavity used is in the range of 0.05 to 25%, preferably in the range of 0.1 to 20%, more preferably in the range of 0.5-15%, an effective inhalation of the drug is ensured in the case that said dry powder formulation is inhaled from capsule.

According to this, in the case that said dry powder formulation is inhaled from capsule, the present invention is characterized in that fullness ratio of capsule cavity is in the range of 0.05 to 25%, preferably in the range of 0.1 to 20%, more preferably in the range of 0.5 to 15%.

In the case that the dry powder formulation of the present invention is inhaled from blister, which is one of the inhalation methods, the inventors have found that an effective inhalation is performed in the case that cavity volume of the blister comprising the drug in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof is in the range of 18-30 mm^3, preferably in the range of 20 - 25 mm^3, more preferably in the range of 21-24 mm^3.

According to this, the present invention is characterized in that cavity volume of the blister used for storage and delivery of the drug in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof is 18-30 mm^3, preferably in the range of 20 to 25 mm^3, more preferably in the range of 21-24 mm^3 in the case that said dry powder formulation is inhaled from blister.

The inventors have found that fullness ratio of the blister cavity used should be in the range of 15-95%, preferably in the range of 20-85% and more preferably in the range of 50-80% in order to inhale the formulation of the present invention from blister without any problem and in order to perform an effective inhalation.

In the case that said dry powder formulation is inhaled from blister, the present invention is characterized in that fullness ratio of the blister used for storage and delivery of the drug in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof is in the range of 15-95%, preferably in the range of 20-85% and more preferably in the range of 50-80%.

In the case that the dry powder formulation of the present invention is inhaled from blister, the base and the lid sheets constituting the peelable blister strip pack, wherein the blisters comprising the dry powder formulation of the present invention are collocated, are sealed tightly by any suitable method in order to provide impermeability.

The base and lid sheets constituting the peelable blister strip package comprising the dry powder formulation of the present invention are composed of many layers. Polymeric layers, aluminium foil and preferably Aclar® fluoropolymer film are among the layers constituting the base and the lid sheets.

The inventors have seen that, in the case that the formulation of the present invention is inhaled from blister, adding desiccant to the polymeric layers in order to reduce moisture and gas permeability of base and lid sheets constituting the blister package is effective in protecting stability of said dry powder formulation. Desiccant agents added to the layers constituting blister strip package comprising dry powder formulation of the present invention are selected from silica gel, zeolite, alumina, bauxite, anhydrous calcium sulphate, activated carbon, hydrophilic chyles.

In the case that dry powder formulation of the present invention is inhaled from blister, polymeric layers in the base and lid sheets of peelable blister strip package comprising said dry powder formulation are made of the same or different polymers. Thickness of these polymeric layers varies depending on the type and characteristics of the polymeric material used. Therefore, thickness of the polymeric layer varies in the range of 15-55 μm, preferably in the range of 20-30 μm according to the type of the polymeric material used.

The layer covering the inner surface of the cavity is a polymeric layer because of the fact that when the layer in contact with the dry powder formulation in the blister cavity is aluminium foil, some part of dry powder formulation adheres to the inner surface of the blister cavity due to

porous structure of the aluminium foil and electrostatic forces and this causes uncontrolled dose inhalation. Polymers constituting the polymeric layer can preferably be selected from thermoplastic polymers such as polyethylene, polypropylene, polystyrene, polyolefin, polyamide, polyvinyl chloride, polyurethane or synthetic polymers.

The drug composition in dry powder form described in the present invention comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof can be used in the treatment of many respiratory diseases particularly asthma, Chronic Obstructive Pulmonary Disease (COPD) and allergic rhinitis. Accordingly, the drug composition of the present invention is used in the treatment of respiratory tract diseases comprising, but not limited to, allergic or non allergic asthma in every stage, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), exacerbation of airways hyperactivity, chronic obstructive pulmonary disease including bronchiectasis, emphysema and chronic bronchitis; airways or lung diseases (COPD, COAD or COLD) pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis. This treatment may be prophylactic or symptomatic. In addition, the composition of the present invention is particularly used in symptomatic treatment of asthma, allergic rhinitis and COPD.

EXAMPLE 1:

Dry powder formulation suitable for a gelatin capsule used in capsule inhaler comprises 1 part of tiotropium, 0.2 part of formoterol fumarate, 20 parts of budesonide; and 275 parts of fine grained lactose and 9.5 parts of coarse grained lactose as carrier, all of which are micronized in an air jet mill.

In obtainment of the formulation that shall be used in said invention, fine grained lactose and coarse grained lactose are stirred in a mixer after sieved separately. Tiotropium, formoterol and budesonide are added to this mixture one by one, sieved again and mixed. The powder mixture obtained at the end of the process is filled into capsules.

The pharmaceutical composition of the present invention can be explained with, but not limited to, these examples.

The example can be repeated by replacing the amounts used in example 1 with the amounts given in the table below.

EXAMPLE	Amount of tiotropium (parts)	Amount of formoterol (parts)	Amount of budesonide (parts)	Amount of fine grained lactose (parts)	Amount of coarse grained lactose (parts)
2	2	0,2	40	19	550
3	2	0,3	36	19	550
4	2	0,36	36	18	560
5	2	0,4	40	18	560
6	2	0,5	44	20	550
7	3	0,48	63	28,5	822
8	3	0,45	57	27	825
9	3	0,6	51	27	819
10	3	0,45	60	28,5	819
11	3	1,5	60	27	831
12	4	1,6	76	38	1100
13	4	2,4	72	36	1100
14	4	2	84	34	1112
15	4	2,8	80	36	1110

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CLAIMS

1. A pharmaceutical formulation in dry powder form comprising tiotropium, formoterol and budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that
   - the ratio of tiotropium, formoterol and budesonide to each other respectively is in the range of 0.5: 0.05: 3 to 1:3:45,
   - the excipient comprised in said formulation is composed of an excipient combination comprising a fine grained excipient having an average particle size less than 10 μm and a coarse grained excipient having an average particle size in the range of 10 μm to 90 μm and
   - the average particle size ratio of the fine grained excipient: the coarse grained excipient is in the range of 1:30 to 1:2.
2. The pharmaceutical formulation according to claim 1, characterized in that the ratio of tiotropium, formoterol and budesonide to each other respectively is in the range of 1:0.1:2 to 1:2:40.
3. The pharmaceutical formulation according to claims 1-2, characterized in that the average particle size ratio of fine grained excipient: coarse grained excipient is in the range of 1:20 to 1:5.
4. The pharmaceutical formulation according to claims 1-3, characterized in that the average particle size ratio of fine grained excipient: coarse grained excipient is in the range of 1:15 to 1:10.
5. The pharmaceutical formulation according to claims 1-4, characterized in that the average particle size of the fine grained excipient is in the range of 0.1 to 9.9 μm.
6. The pharmaceutical formulation according to claims 1-5, characterized in that the average particle size of the fine grained excipient is in the range of 2 to 8 μm.
7. The pharmaceutical formulation according to claims 1-6, characterized in that the average particle size of the fine grained excipient is in the range of 0.3, 0.5, 0.7, 0.9, 1.1, 1.3, 1.5, 1.7, 1.9, 2.3, 2.5, 3.0, 3.5, 4.0, 4.5 to 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5 μm.
8. The pharmaceutical formulation according to claims 1-7, characterized in that the average particle size of the coarse grained excipient is in the range of 12 to 85 μm.
9. The pharmaceutical formulation according to claims 1-8, characterized in that the average particle size of the coarse grained excipient is in the range of 15 to 80 μm.

10. The pharmaceutical formulation according to claims 1-9, characterized in that the average particle size of the coarse grained excipient is in the range of 20, 25, 30, 35, 40, 45 to 50, 55, 60, 65, 70, 75, 80, 85 μm.
11. The pharmaceutical formulation according claims 1-10, wherein tiotropium and/or pharmaceutically acceptable derivatives thereof comprise tiotropium's free base, pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or a combination thereof.
12. The pharmaceutical formulation according claims 1-11, wherein formoterol and/or pharmaceutically acceptable derivatives thereof comprise formoterol's free base, pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or a combination thereof.
13. The pharmaceutical formulation according claim 12, wherein formoterol is used in formoterol fumarate form.
14. The pharmaceutical formulation according claims 1-13, wherein budesonide and/or pharmaceutically acceptable derivatives thereof comprise budesonide's free base, pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms and/or a combination thereof.
15. The pharmaceutical formulation according to claims 1-14, wherein the fine grained and the coarse grained excipients are selected from monosaccharides (glucose), disaccharides (lactose, saccharose, maltose or pharmaceutically acceptable hydrates, solvates, anhydrous forms or a combination thereof), oligosaccharides and polysaccharides (dextrant), polyalcohols (sorbitol, mannitol, xylitol), salts (sodium chloride, calcium carbonate) or a combination thereof.
16. The pharmaceutical formulation according to claims 1-15, wherein the fine grained and the coarse grained excipients are selected from the same or different substances.
17. The pharmaceutical formulation according to claims 1-16, wherein lactose or a pharmaceutically acceptable hydrate, anhydrate or a combination thereof is used as fine grained excipient and coarse grained excipient.
18. The pharmaceutical formulation according to claims 15-17, wherein lactose anhydrate is used as fine grained excipient and coarse grained excipient.

19. The pharmaceutical formulation according to claims 1-18, wherein the total amount of the pharmaceutically acceptable excipient is in the range of 1-50 mg.
20. The pharmaceutical formulation according to claim 19, wherein the total amount of the pharmaceutically acceptable excipient is in the range of 2-40 mg.
21. The pharmaceutical formulation according to claim 20, wherein the total amount of the pharmaceutically acceptable excipient is in the range of 3-30 mg.
22. The pharmaceutical formulation according to claims 1-21, wherein the average particle size of the active agents comprised in said formulation is in the range of 1 μm to 10 μm.
23. The pharmaceutical formulation according to claim 22, wherein the average particle size of the active agents comprised in said formulation is in the range of 1.5 μm to 7.5 μm.
24. The pharmaceutical formulation according to claim 23, wherein the average particle size of the active agents comprised in said formulation is particularly in the range of 1.5 μm to 5 μm.
25. The pharmaceutical formulation according to claims 1-24, wherein the ratio of fine grained excipient to coarse grained excipient is in the range of 1:1 to 1:25 by weight.
26. The pharmaceutical formulation according to claim 25, wherein the ratio of fine grained excipient to coarse grained excipient is in the range of 1:1 to 1:10 by weight.
27. The pharmaceutical formulation according to claim 26, wherein the ratio of fine grained excipient to coarse grained excipient is in the range of 1:1.5 to 1:5 by weight.
28. A process in order to prepare the pharmaceutical formulation according to claims 1-27, characterized in that said process is composed of the steps of:
    I. micronizing tiotropium, formoterol and budesonide so as to bring them to the desired particle size,
    II. micronizing the excipients together or separately in order to bring them to the desired particle size,
    III. mixing the active agents micronized in step I firstly with the fine grained excipient and then with the coarse grained excipient in a mixer or firstly with the coarse grained excipient and then with the fine grained excipient in a mixer and
    IV. consequently, filling the mixture obtained in dry powder form into suitable capsules, blisters or reservoirs and making it ready for use.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000032

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/381 A61K31/46
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/093817 A1 (BILGIC MAHMUT [TR]) 4 August 2011 (2011-08-04) claims 1-28	1-28
Y	WO 2011/093812 A2 (BILGIC MAHMUT [TR]) 4 August 2011 (2011-08-04) claims examples	1-28
Y	WO 2008/102128 A2 (CIPLA LTD [IN]; CURTIS PHILIP ANTHONY [GB]; LULLA AMAR [IN]; MALHOTRA) 28 August 2008 (2008-08-28) page 32; example 43	1-28
Y	WO 2004/019985 A1 (CIPLA LTD [IN]; LULLA AMAR [IN]; MALHOTRA GEENA [IN]; WAIN CHRISTOPHER) 11 March 2004 (2004-03-11) examples 34-43	1-28

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 2013	24/06/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Schüle, Stefanie

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2013/000032

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011093817 A1	04-08-2011	EP 2528585 A1	05-12-2012
		TR 201000680 A2	22-08-2011
		WO 2011093817 A1	04-08-2011
WO 2011093812 A2	04-08-2011	NONE	
WO 2008102128 A2	28-08-2008	AU 2008217586 A1	28-08-2008
		CA 2677573 A1	28-08-2008
		CL 5002008 A1	05-09-2008
		EP 2124915 A2	02-12-2009
		EP 2327403 A2	01-06-2011
		JP 2010519195 A	03-06-2010
		KR 20090121338 A	25-11-2009
		PE 17882008 A1	18-12-2008
		US 2010063016 A1	11-03-2010
		US 2013074834 A1	28-03-2013
		WO 2008102128 A2	28-08-2008
WO 2004019985 A1	11-03-2004	AU 2003260754 A1	19-03-2004
		CA 2496699 A1	11-03-2004
		EP 1531866 A1	25-05-2005
		EP 2319582 A1	11-05-2011
		EP 2319583 A1	11-05-2011
		EP 2319584 A1	11-05-2011
		EP 2319585 A1	11-05-2011
		EP 2322243 A1	18-05-2011
		EP 2329861 A1	08-06-2011
		JP 2005539046 A	22-12-2005
		NZ 538493 A	26-10-2007
		RU 2327450 C2	27-06-2008
		US 2006035874 A1	16-02-2006
		WO 2004019985 A1	11-03-2004