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(54) Title: DRY POWDER FORMULATIONS COMPRISING BUDESONIDE

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

DRY POWDER FORMULATIONS COMPRISING BUDESONIDE

The present invention relates to pharmaceutical formulations in dry powder form comprising budesonide 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.

Budesonide is used in the treatment of respiratory tract diseases such as asthma and COPD. Budesonide which has the chemical name of 16,17-(butylidenebis(oxy))-11,21-dihydroxy-, (11-β,16-α)-pregna-1,4-diene-3,20-dione belongs to the group of corticosteroids. Budesonide was first disclosed in the patent numbered US3929768.

Corticosteroids used in the treatment of respiratory tract diseases such as 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 is a molecule which belongs to said group.

The fact that the dry powder formulation comprising budesonide 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 agent cannot reach to the lungs in sufficient amounts.

In order to ease the delivery of the active agent having therapeutic effect in quite small doses by the inhalation route, the active agent is 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 agent used is delivered to the lungs in a sufficient amount 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 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 budesonide and/or pharmaceutically acceptable derivatives thereof.

Surprisingly, the inventors have seen that dry powder formulations comprising budesonide in the range of 25 to 650 µg, preferably in the range of 50 to 500 µg 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 budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that

the amount of budesonide in said formulation is in the range of 25 to 650 μg, preferably in the range of 50 to 500 μg,

- 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, the inhalation formulation comprising 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 an active agent 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 budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that

- the amount of budesonide in said formulation is in the range of 25 to 650 μg, preferably in the range of 50 to 500 μg,
- 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 agent 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.

In addition to the average particle size of the active agent, the particle size of the bulk formulation is also an important criteria for the flowability and dose uniformity of the formulation. The inventors have seen that in the case that the average particle size (d50 value) of the bulk formulation is in the range of 10-100 μm, preferably 20-90 μm and more preferably 25-75 μm, flowability of the bulk formulation is increased during the production and a homogeneous dry powder formulation which has a high dose uniformity is obtained.

In another aspect, the present invention relates to the pharmaceutical formulations in dry powder form comprising budesonid and/or pharmaceutically acceptable derivatives thereof wherein the average particle size (d50 value) of the bulk formulation is in the range of 10-100 μm, preferably 20-90 μm and more preferably 25- 75 μm.

It is seen that d10 and d90 values of the bulk formulation have also an influence on providing an appropriate flow and thus the dose uniformity of the formulation. The inventors have observed that when the bulk formulation obtained during the production has d10 value in the range of 2-40 μm, preferably 5- 30 μm and has d90 value in the range of 60- 150 μm, preferably 75- 125 μm, the formulation has a high dose uniformity and a more effecient treatment can be provided.

In another aspect, the present invention relates to the pharmaceutical formulations in dry powder form comprising budesonid and/or pharmaceutically acceptable derivatives thereof wherein the bulk formulation obtained during the production has d10 value in the range of 2-40 μm, preferably 5- 30 μm and has d90 value in the range of 60- 150 μm, preferably 75- 125 μm.

The term bulk formulation used herein signifies that the total formulation obtained by mixing the active agent and the excipients during the production.

The term d10 used herein signifies that 10% of the formulation by volume has a particle size below the value stated with d10.

The term d10 used herein signifies that 10% of the formulation by volume has a particle size below the value stated with d50.

The term d90 used herein signifies that 90% of the formulation by volume has a particle size below the value stated with d90.

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 budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that

- the amount of budesonide in said formulation is in the range of 25 to 650 μg, preferably in the range of 50 to 500 μg,
- 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.

It is known that flowability is an important parameter for obtaining a homogeneous mixture of the active agent and the excipients during the production and providing dose uniformity of the formulation and thus minimizing the amount of the active agent remained in the device. The parameters such as bulk density and tapped density have a considerable influence on providing good flowability. The inventors have provided the dry powder formulation to have a good flowability by adjusting the bulk density and tapped density in the manner that the ratio of bulk density to tapped density is in the range of 1:10 to 9.5:10, preferably 2:10 to 9:10, more preferably 3:10 to 9:10.

In another aspect, the present invention relates to the pharmaceutical formulations in dry powder form comprising budesonid and/or pharmaceutically acceptable derivatives thereof wherein the ratio of bulk density to tapped density is in the range of 1:10 to 9.5:10, preferably 2:10 to 9:10, more preferably 3:10 to 9:10.

The tapped density is obtained by compacting the bulk density with vibrational motion.

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

I. micronizing budesonide so as to bring it to the desired particle size,
II. micronizing the excipient so as to bring it to the desired particle size,
III. mixing the active agent 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 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 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 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 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 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 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 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 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 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: Inhalation of dry powder formulations comprising budesonide from capsule

Formulation content	**% of amount by weight**
Budesonide	0.4 %
Fine grained lactose	29.6 %
Coarse grained lactose	70 %

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. Budesonide is added into this mixture, sieved again and stirred. The powder mixture obtained at the end of the process is filled into capsules.

EXAMPLE 2: Inhalation of dry powder formulations comprising budesonide from capsule

Formulation content	**% of amount by weight**
Budesonide	0.5 %
Fine grained lactose	33 %
Coarse grained lactose	66.5 %

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. Budesonide is added into this mixture, sieved again and stirred. The powder mixture obtained at the end of the process is filled into capsules.

CLAIMS

1. A pharmaceutical formulation in dry powder form comprising budesonide and/or pharmaceutically acceptable derivatives thereof, characterized in that
   - the amount of budesonide in the formulation is in the range of 25 to 650 μg,
   - 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 amount of budesonide in the formulation is in the range of 50 to 500 μg.
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 budesonide and/or pharmaceutically acceptable derivatives thereof comprise its 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 to claims 1-11, 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.
13. The pharmaceutical formulation according to claims 1-12, wherein the fine grained and the coarse grained excipients are selected from the same or different substances.
14. The pharmaceutical formulation according to claims 1-13, wherein lactose or a pharmaceutically acceptable hydrate, anhydrate or a combination thereof is used as fine grained excipient and coarse grained excipient.
15. The pharmaceutical formulation according to claims 12-14, wherein lactose anhydrate is used as fine grained excipient and coarse grained excipient.
16. The pharmaceutical formulation according to claims 1-15, wherein the total amount of the pharmaceutically acceptable excipient is in the range of 1-50 mg.
17. The pharmaceutical formulation according to claim 16, wherein the total amount of the pharmaceutically acceptable excipient is in the range of 2-40 mg.
18. The pharmaceutical formulation according to claim 17, wherein the total amount of the pharmaceutically acceptable excipient is in the range of 3-30 mg.
19. The pharmaceutical formulation according to claims 1-18, wherein the average particle size of the active agent comprised in said formulation is in the range of 1 μm to 10 μm.
20. The pharmaceutical formulation according to claim 19, wherein the average particle size of the active agent comprised in said formulation is in the range of 1.5 μm to 7.5 μm.
21. The pharmaceutical formulation according to claim 20, wherein the average particle size of the active agent comprised in said formulation is particularly in the range of 1.5 μm to 5 μm.
22. The pharmaceutical formulation according to claims 1- 21 wherein the average particle size (d50 value) of bulk formulation is in the range of 10-100 μm.

23. The pharmaceutical formulation according to claim 22 wherein the average particle size (d50 value) of the bulk formulation is in the range of 20-90 μm.
24. The pharmaceutical formulation according to claim 22- 23 wherein the average particle size (d50 value) of the bulk formulation is in the range of 25- 75 μm.
25. The pharmaceutical formulation according to claims 1- 24 wherein bulk formulation obtained during the production has d10 value in the range of 2-40 μm and has d90 value in the range of 60- 150 μm.
26. The pharmaceutical formulation according to claim 25 wherein the bulk formulation obtained during the production has d10 value in the range of 5- 30 μm and has d90 value in the range of 75- 125 μm.
27. The pharmaceutical formulation according to claims 1-21, wherein the ratio of fine grained excipient to coarse grained excipient is in the range of 1:1 to 1:25 by weight.
28. The pharmaceutical formulation according to claim 22, wherein the ratio of fine grained excipient to coarse grained excipient is in the range of 1:1 to 1:10 by weight.
29. The pharmaceutical formulation according to claim 23, wherein the ratio of fine grained excipient to coarse grained excipient is in the range of 1:1.5 to 1:5 by weight.
30. The pharmaceutical formulation according to claims 1- 29 wherein ratio of bulk density to tapped density is in the range of 1:10 to 9.5:10.
31. The pharmaceutical formulation according to claim 30 wherein the ratio of bulk density to tapped density is in the range of 2:10 to 9:10.
32. The pharmaceutical formulation according to claims 30- 31 wherein the ratio of bulk density to tapped density is in the range of 3:10 to 9:10.
33. A process for preparation of the pharmaceutical formulation according to claims 1-24, characterized in that said process is composed of the steps of:
    I. micronizing budesonide so as to bring it 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 agent 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/TR2013/000022

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K31/58
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 2011/093812 A2 (BILGIC MAHMUT [TR]) 4 August 2011 (2011-08-04)	1,2,5-32
Y	claims page 5, line 13 - line 24	1-33

X	WO 2011/093817 A1 (BILGIC MAHMUT [TR]) 4 August 2011 (2011-08-04)	1-32
Y	page 6, paragraph 4 - paragraph 5	1-33

Y	US 2003/180227 A1 (STANIFORTH JOHN NICHOLAS [IT] ET AL) 25 September 2003 (2003-09-25) claims 1-14	1-33

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

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2013	27/05/2013

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

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