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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING FORMOTEROL AND MOMETASONE

(57) Abstract: The present invention relates to pharmaceutical compositions in dry powder form comprising formoterol and mometasone froate and/or their pharmaceutically acceptable derivatives as active agents, and capsule and blister forms containing these pharmaceutical compositions so as to be used in treatment of respiratory tract diseases.

PHARMACEUTICAL COMPOSITIONS COMPRISING FORMOTEROL AND MOMETASONE

The present invention relates to a pharmaceutical composition in dry powder form comprising formoterol and mometasone and/or their pharmaceutically acceptable derivatives as active agents so as to be used in the treatment of respiratory tract diseases especially in asthma and chronic obstructive pulmonary disease (COPD), and the delivery of this pharmaceutical composition.

Formoterol, which has the chemical name (+/-)-2-Hidroksi-5-((RS))-1-hidroksi-2-{((RS)-p-metoksi-alfametilfenil)amino}etil)-formanilid, is a long-acting broncodilator. Formoterol and its pharmaceutically acceptable, nontoxic salts were first disclosed in the patent numbered US 3994974 by Yamanouchi in 1973. The original drug containing formoterol alone belongs to Novartis under the name Foradil.

The molecules which are generally known as β_2-adrenergic agonists in pharmacology including formoterol present local effects and they lead to open the bronchia by causing relaxation of smooth muscles around the air vessels. With the help of this property, these drugs are used in the treatment of asthma and chronic obstructive pulmonary disorder (COPD). The effect of these drugs, which starts in several minutes following the inhalation, is still evident after 12 hours.

In 2005, US Food and Drug Administration (FDA) revealed that many long-acting β_2-agonist drugs increase wheezing symptom in patients. Following this, in a study carried out by Cornell and Stanford Universities in 2006, it was found out that continuous and/or high doses of β-agonists intake in the treatment of COPD increases health problems resulting from respiratory tract. As can be seen, different methods should be applied in the use of β_2-agonists in the treatment of asthma and COPD.

Mometasone furoate, which has the chemical name (11β, 16α)-9,21-dikloro-17-[(2-furanilkarbonil)oksi]-11-hidroksi-16-metil-pregna-1, is an anti-flammatory corticosteroid. The molecule mometasone furoate was first disclosed in the patent numbered US4472393. The original product containing mometasone is Asmanex Twisthaler which belongs to Schering-Plough.

Another group of drugs including mometasone which is commonly used in the treatment of asthma and COPD are known as corticosteroids in pharmacology. The molecules included in

this group lead to open the airways by controlling inflammation that underlie asthma and reducing mucus secretion, and therefore eliminate the complications of the patients suffering from asthma. In the case of systemic intake of the drugs in this group, they cause very serious side effects such as osteoporosis, high cholesterol, edema, headache, weight gain, sleeping disorders, various skin problems and growth retardation in children. Therefore, the administration methods in which the least possible amount of the drug enters the systemic circulation are preferred. This type of molecules are administered by the inhalation route in the treatment of asthma to reduce the side effects and to convey the highest possible dose to the lungs.

As mentioned above, the drugs containing β2-agonist have the potential to trigger respiratory disorders. The combination of these substances, which are inevitable to use in the treatment of asthma, with other different substances that are effective on the same disease is beneficial in terms of reducing the amount of β_2-agonist intake, thus the frequency of the side effects and the benefits that the patients would gain from the synergic effect of the combination of two different active agents. To this respect, it was found out that the use of β_2-agonists in combination with corticosteroids is beneficial as this provides to reduce the amount of β_2-agonist to be taken; to open the bronchia with the positive effect of β_2-agonists thus to control the symptoms; and to prevent the inflammation which causes asthma with the use of corticosteroids.

Ideally, the administration methods which enable to convey the therapeutic drugs rapidly and directly to the target area; to show the desired effect at lower doses and therefore to alleviate and/or eliminate the side effects are preferred in the transmission of the drugs that show therapeutic effects in body. Taking the very serious side effects of systemic intake of corticosteroids into consideration, it is seen how important it is to transmit this combination effectively. One of the problems that is mostly emphasized in the prior art is the development of these transmission methods and devices.

The use of combination drugs in the treatment of respiratory diseases such as asthma and COPD is very effective particularly in decreasing asthma attacks. It is possible that the severity or occurrence possibility of the abovementioned side effects decreases as the active substances that are used in combinations are more effective at lower doses compared to the active substances used alone

However, decreasing the side effects that arise from the active agents is not sufficient to provide an effective treatment for respiratory diseases. Medicaments used in the formulations should be selected in a way to give the best combination and furthermore they should be in the most stable form. Moreover, the compositions comprising them should be formulated in such a way that the composition is stable and also it reaches to the target area in the most efficient way.

The inventor has found that therapeutic benefits are obtained through the use of the combination comprising formoterol fumarate and mometasone froate together in dry powder form for simultaneous or sequential administration in the prevention or treatment of respiratory diseases.

It was seen that a combination comprising formoterol fumarate and mometasone froate in dry powder form provides the most stable and therapeutically beneficial combination for simultaneous or sequential administration in the prevention or treatment of respiratory diseases.

Furthermore, the amount of active agents used in the composition is carefully adjusted in order to prevent side effects that might arise from these agents and it was seen that the adhesive force between the particles forming the composition is reduced and hence, the amount of inhaled particles and efficacy of the formulation increases in addition to observing minimum side effects, when formoterol fumarate and mometasone froate present in the composition is used in an amount that the ratio of formoterol fumarate to mometasone froate is in the range of 1:15 to 1:95 by weight.

In order to ensure effective absorption of the active agents into the lung tissue, the particle size of the agents should be adjusted. Although large particle size provides ease in the manufacture of the dry powder, it may accumulate in throat and lead to insufficient intake of the medicament. Very fine particles on the other hand, may reach the lungs. However, they might not have a good flow property which in turn causes problems in providing dose accuracy. To prevent these problems, the active agents should have an optimum average particle size. Inventors have found that formoterol fumarate and mometasone froate combination wherein the mean particle size of the active agents is in the range of 1.5 to 4.5 μm reaches lungs effectively and also no problems related to flow properties of the dry powder are observed.

The term "mean particle size" refers to particles wherein the size of 50% of the total number of particles is less than the average particle size.

In one aspect, present invention is related to dry powder formulations comprising a combination of formoterol fumarate and mometasone froate in dry powder form wherein formoterol fumarate and mometasone froate is present in the composition in an amount such that the ratio of formoterol fumarate and mometasone froate is in the range of 1:15 to 1:95 by weight and wherein the mean particle size of the active agents (i.e. formoterol fumarateand mometasone froate) is in the range of 1.5 to 4.5 μm.

According to the present invention, the drug comprising formoterol fumarate and mometasone froate may also contain effective amounts of excipients and/or additional agents apart from active agents.

According to the present invention, the dry powder formulation containing formoterol fumarate and mometasone froate is transmitted to the patient in dry powder form. Said dry powder formulations also contain some physiologically acceptable excipients along with the active agent. These excipients can be monosaccharides (glucose, etc.), disaccharides (lactose, saccharose, maltose, etc.), oligosaccharides and polysaccharides (dextran, etc.), polyalcohols (sorbitol, mannitol, xylitol, etc.), salts (sodium chloride, calcium carbonate, etc.) or a mixture thereof.

Inventors have found that in compositions according to present invention, in other words in compositions comprising formoterol fumarateand mometasone froate in dry powder form wherein mean particle size of formoterol fumarateand mometasone froateis in the range of 1.5 to 4.5 μm and wherein formoterol fumarate and mometasone froate are present in the composition in an amount that the ratio of formoterol fumarate to mometasone froate is in the range of 1:15 to 1:95 by weight, using lactose as the one and only carrier provides optimum homogeneity and flow properties to the dry powder and this way dose accuracy is maintained.

In other words, it is another aspect of the present invention that lactose is used as the one and only carrier in dry powder formulations comprising combinations of formoterol fumarate and mometasone froate in dry powder form.

It was seen that the mean particle size of the lactose plays an important role in delivery of the medicament to the target area, i.e. lungs, effectively in the compositions according to the

present invention. It was found that the adhesive forces present between the lactose particles and the active agents having the mean particle size in the range of 1.5 to 4.5 μm are minimized and thus an effective inhalation of the active agents takes place when lactose which has a mean particle size less than or equal to 100 μm is used in the compositions comprising formoterol fumarate and mometasone froate in dry powder form wherein the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and wherein said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively.

It was also seen that in the compositions pertaining to the present invention, the total water content of the lactose has a considerable effect on the stability of lactose and the drug. It was found that when lactose with total water content in the range of 4%-6% is used in compositions comprising formoterol fumarate and mometasone froate in dry powder form wherein mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and wherein said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively, lactose shows a highly stable behavior and thus long term stability of the drug is maintained.

In another aspect, the present invention provides a composition comprising formoterol fumarate and mometasone froate in dry powder form wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and water content in the range of %4-%6 is used as carrier.

Lactose which has mean particle size less than 100 μm is preferably used as a mixture of particles which have two different mean particle sizes. Accordingly, lactose which has a mean particle size less than 100 μm can be present as a mixture of particles having a mean particle size less than 10 μm (fine) and particles having a mean particle size in the range of 10 μm to 100 μm (coarse). The inventors have observed that the adhesive force between the active agents and lactose is even less when lactose which has two different mean particle sizes is used.

Accordingly, the fine lactose particles have a mean particle size less than 10 μm, preferably between 2 μm and 8μm, and the coarse lactose particles have a mean particle size less than 100 μm, preferably between 30 μm and 80 μm.

The ratio between the fine lactose particles which have a mean particle size less than 10 μm and the coarse lactose particles which have a mean particle size in the range of 10 μm to 100 μm is in the range of 20:80% to 40:60% by weight.

According to the present invention, the amount of pharmaceutically acceptable carrier is preferably in the range of 0-50 mg. The medicament combination of the present invention is in dry powder form and it is inhaled via dry powder inhalers. Accordingly, the medicament can be inhaled via inhalators including a reservoir containing dry powder; a blister pack in which many blisters are placed in an order or capsules. Among these, the inhalers that enable the intake of a single dose in an accurate manner were found to give the best results. This condition is provided by the dosage forms wherein each dose of the medicament is stored in a single unit of dosage form. Accordingly, medicament combination according to present invention is stored in blister packs consisting of blisters or capsules and is inhaled through dry powder inhalation devices where blisters or capsules are used.

The inventor has surprisingly found that administering the dry power drug containing formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and water content in the range of %4-%6 is used as carrier

as stored in a blister packs or capsules via a dry powder inhaler in order to prevent and treat respiratory diseases provides the transmission of the exact and the effective dose to the target area and elimination and/or alleviation of the known side effects of the therapeutic agents. Hence, maximum therapeutic benefit is provided due to the efficacy of the transmission method.

According to another aspect, the present invention provides a dry powder drug containing the combination of formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier

which realizes a simultaneous inhalation from the blister packs or capsules that can guarantee a single dose intake at once in order to achieve dose sufficiency.

According to another aspect, the present invention provides the inhalation of the dry powder drug containing the combination of formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier

via a simple, low cost, trustable dry powder inhaler.

According to another aspect, the present invention provides a drug that provides to realize the use of a composition comprising formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and

lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier as stored together in a peelable blister or pierceable capsule packs in the treatment of respiratory diseases such as asthma and COPD.

The inventors have found that by storing the dry powder medicament pertaining to the present invention in blister packs comprising blisters and capsules which have the specified properties pertaining to the present invention;

- equal dose intake is provided in each use as the dry powder formulation is filled into the blisters or capsules with a good dosage accuracy in the factory after the manufacture,
- the drug is transmitted to the target area, which is the lungs, without absorbing moisture as the blister or capsule pertaining to the present invention is peeled/torn/pierced immediately before use,
- inhalation of inadequate or excessive dose is prevented and inhalation of a unit dose is ensured as it is single dose,
- the dry powder formulation pertaining to the present invention is effectively transmitted to the lungs from the blisters or capsules pertaining to the present invention via a dry powder inhaler, and
- devices containing blisters or capsules provide ease of use to the patients as they are small in size resulting from the fact that they work with simple mechanical components compared to other devices.

The present invention relates to a delivery method of a drug composition containing a composition comprising formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier

which is particularly used in the treatment of people suffering respiratory diseases such as asthma, COPD and allergic rhinitis, as stored in a blister or capsule package via a dry powder inhaler.

If capsule is used as the package for the dry powder medicament according to the invention, the piercing components, which exist in the device to prepare the dry powder drug carried in a capsule for inhalation, pierce the capsule when the device is triggered and the dry powder drug kept in the capsule gets ready for inhalation. After the inhalation is completed, the empty

capsule is ejected from the device and a new capsule is placed immediately before the following inhalation takes place.

The capsule package, which is preferred to be used in scope of the present invention, consists of two intertwining parts.

In the present invention, the inventors have found that the ideal inhalation conditions are achieved when the volume of the capsule, which comprises the dry powder drug containing formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and

lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier, is in the range of 0.1 to 0.52 ml, preferably in the range of 0.1 to 0.45 ml, more preferably in the range of 0.15 to 0.42 ml. Accordingly, the capsule that is used to store and transmit the combination comprising formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier,

is characterized in having a cavity volume in the range of 0.1 to 0.52 ml, preferably 0.1 to 0.45 ml, more preferably in the range of 0.15 to 0.42 ml.

According to another aspect, the capsule package which has high protection against moisture and other negative external factors has a moisture rate between 10%-20%, preferably 15%-20%. In the case that the capsules having this characteristic are used, both the active composition is protected from external factors and the probability of moisture arising from the capsule's own structure are prevented. Thus, the most effective transmission to the patient is enabled by preventing the agglomeration of the dry powder.

The capsule, which is preferred to be used in scope of the present invention, can be made of a substance chosen from a group including gelatine, chitosan, starch and/or starch derivatives, cellulose and/or cellulose derivatives or synthetic polymers as well as consisting intertwined upper and lower parts. These upper and lower parts of said capsule can be produced of identical or different materials.

In the case that the capsule used in the present invention is made of cellulose or its derivatives, the capsule material can be selected from, but not limited to, a group comprising hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose.

In the case that the capsule used in the present invention is synthetic polymer, the capsule material can be selected from, but not limited to, a group including polyethylene, polyetheleneteraphtalate, polycarbonate or polypropylene.

In the case that the capsule material used in the present invention is gelatine, additional agents such as polyethylene glycol, sorbitol, glycerol, propylene glycol, polyethylene oxide - polypropylene oxide block copolymers and/or other polyalcohols or polyethers at different molecular weights can be added into it.

According to another aspect, the present invention is characterized in that the capsule cavity used to provide an effective inhalation of the dry powder medicament is filled up to 0.01% to 25% of its total volume, preferably 0.1 to 20% of its total volume, more preferably 0.5 to 17% of its total volume.

According to this, the present invention comprises dry powder formulations comprising formoterol fumarate and mometasone froate and/or pharmaceutically acceptable derivatives and their administration to patients from a capsule having a total cavity volume in the range of 0.1 to 0.52 ml wherein the capsule cavity is filled up to 0.01% to 25% of the total volume, via a dry powder inhaler.

In addition, the capsule pack pertaining to the present invention can be in any color or shape as long as it has the properties described above.

The capsule or the blister pack, which comprises the formulation pertaining to the present invention, can be used with any dry powder inhalation device, for example with devices as

described in the patent applications numbered TR2008/03522, TR2008/03523, TR2010/03091, TR2010/04311.

In another aspect, blister packs can be used as the package for the dry powder medicament according to the invention. Blister packages can be a) torn b) pierced or c) peeled to be opened according to the structure of the device and the blister. As a result of studies and experiments that they conducted, the inventors have found that it is difficult to use dry powder inhalers which contain pierceable or tearable blister packs for patients as these devices require additional components which increase the size, volume and the complexity of the device. In addition, the amount of uninhaled dry powder formulation remaining in the blister cavity increases due to the roughness resulting from being torn and therefore, the rate of utilization from the present dry powder formulation decreases in tearable blisters. In contrast, the amount of dry powder remaining in the blister cavity decreases as said dry powder combination is transmitted much more effectively with a high discharge capacity in the case that peelable blisters are used.

The dry powder medicament pertaining to the present invention can be carried in peelable blister packages. Blister packs are comprised of orderly placed blisters each of which contains minimally one dose of the dry powder drug. When the device is triggered, the blister pack or one of the blisters in the pack is peeled and the drug in dry powder form is prepared for inhalation.

According to the present invention, the cavity volume of the blisters that are arranged side by side in a certain order on the blister pack which provides to carry and store the drug in dry powder from is 17 to 30 mm^3, preferably 18 to 23 mm^3, most preferably 19 to 21 mm^3.

The cavity volume of the blisters pertaining to the present invention, which provide to transmit and store the dry powder drug comprising formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and

lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier, is in the range of 17-30 mm^3, preferably in the range of 18-23 mm^3,

most preferably in the range of 19-21 mm^3 and each blister cavity having the volume described above is filled up to 25-100 %, preferably up to 70-100 %, most preferably up to 90-100 % of said volume in order to meet the specified needs for an effective inhalation.

The lid and the base sheets of said blister pack constituted by the blisters having the specified properties, in which the drug in dry powder form pertaining to the present invention is stored, are closed very tightly by any suitable method to provide impermeability.

According to the present invention, the lid and the base sheets constituting the blister package consist of several layers. Polymeric layers, aluminum foil and preferably Aclar® fluoropoylmer film are among the layers that form the lid and the base sheet.

Aclar® fluoropolymer film is a polymeric film which is used in blister packs and provides excellent moisture barrier. This chemically inert polymeric film does not cause any change in the taste of the formulation when it is in contact with the dry powder formulation. In addition, it easily constitutes a layered structure with the other polymeric layers which are composed of various polymers. It is appropriate to be transacted with heat.

In order to decrease gas and moisture permeability of the layer, preferably desiccant agents are added to the polymeric layers to preserve the stability of the dry powder formulation stored in blisters that are arranged in an order on the blister package. Silica gel, zeolite, alumina, bauxite, anhydrous calcium sulfate, activated carbon and clay which have the property of water absorption can be given as examples to desiccant agents.

As it is common to use aluminum in lid and base sheets of high protection blister packs, aluminum is used both in the lid and the base sheets of the blister pack of the present invention in order to provide high moisture and gas protection. These aluminum foils must be thick enough to provide the desired protection for the stability of the moisture sensitive dry powder formulation stored in the blister cavity. Due to this reason, the thickness of the aluminum foil that is used in the lid and the base sheets of the blister pack is chosen to be in the range of 10 to 40 μm, preferably of 15 to 30 μm.

According to the present invention, the polymeric layers in the lid and the base sheets of the blister pack mentioned in the present invention are composed of the same or different polymers. The thickness of these polymeric layers varies according to the type of the polymeric substance used and its properties. Therefore, the thickness of the polymeric layer

varies in the range of 15-60 μm, preferably of 20-35 μm depending on the type of the polymer used.

The blisters which constitute the blister pack in which the dry powder drug pertaining to the present invention is stored can be in any shape as long as they have the properties described above.

Due to the electrostatic interactions between the dry powder particles and the inside layer of the blister cavity or the capsule material which is in contact with the dry powder formulation, the dry powder particles mainly adhere to said inside layer of the blister cavity or said capsule material. Since some uninhaled dry powder formulation is remained in the blister cavity or the capsule during inhalation, sufficient amount of the dry powder formulation for an effective therapy cannot reach to the lungs. Therefore, the inside layer of the blister cavity or the capsule material that is in contact with the dry powder formulation is an antistatic material. Within the scope of the invention, the term "antistatic material" refers to a material which eliminates the buildup of static electricity. The antistatic material used herein encloses a material which is antistatic itself or which is not antistatic itself but contains antistatic agent(s).

According to the present invention, an antistatic agent is used for treatment of the layer or their surfaces in order to reduce or eliminate the buildup of static electricity generally caused by the triboelectric effect (charge generation by friction). Its role is to make the surface or the material itself slightly conductive, either by being conductive itself, or by absorbing moisture from the air. Therefore, some humectants can be used. The molecules of an antistatic agent often have both hydrophilic and hydrophobic areas similar to those of a surfactant. The hydrophobic side interacts with the surface of the material while the hydrophilic side interacts with the air moisture and binds the water molecules.

Antistatic agents are basically classified into two groups: internal antistatic agents and external antistatic agents. Internal antistatic agents are designed to be mixed directly into the material whereas external antistatic agents are applied to the surface.

Antistatic agents used within the scope of the invention are selected from a group comprising long-chain aliphatic amines (optionally ethoxylated) and amides, glycerol monostearate (GMS), saturated fatty acids, (poly)unsaturated fatty acids, quaternary ammonium salts (e.g., behentrimonium chloride or cocamidopropyl betaine), sulfonated organic compounds, esters

of phosphoric acid, polyethylene glycol esters, or polyols and combinations thereof. Also, some commercialy available antistatic additives such as OnCap™, Larostat ®, Entira™, Nourymix®, can be used as antistatic agents. It is also possible to use conductive polymers like PEDOT:PSS and conducting polymer nanofibers, particularly polyaniline nanofibers.

Processing conditions, polymer base, relative humidity of the environment, material thickness and active agents used in the dry powder formulation play an important role in selecting the most appropriate antistatic agent. Also, the bloom rate (the rate of migration of the antistatic agent to the surface) varies greatly among the antistatic agent choices. The antistatic agents in the material, which is the inside layer of the blister cavity or capsule material, are present in a range from 0,1% to 5% by weight of said material.

In another aspect, the present invention provides a medicament containing a composition comprising formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier

as stored in capsules or blisters wherein the inside layer of the blister cavity or the capsule material that is in contact with the dry powder formulation is an antistatic material. According to the present invention, formoterol fumarate which is one of the active agents of the medicament formulation containing the active agent combination includes its pharmaceutically acceptable solvates, polymorphs, crystal forms, amorphous forms and/or combinations thereof.

According to the present invention, mometasone froate which is one of the active agents of the medicament formulation containing the active agent combination includes its pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, free base, polymorphs, crystal forms, amorphous forms and/or combinations thereof.

According to the present invention, the amount of formoterol fumarate is in the range of 1 to 30μg, preferably in the range of 1 to 20 μg in the medicament formulation in dry powder form

containing the combination of formoterol fumarate and mometasone froate and/or pharmaceutically acceptable derivatives thereof.

According to the present invention, the amount of mometasone froate in the range of 50 to 600μg, preferably in the range of 150 to 500 μg in the medicament formulation in dry powder form containing the combination of formoterol fumarate and mometasone froate and/or pharmaceutically acceptable derivatives thereof.

The dry powder drug containing formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier

as stored in capsules or blisters wherein the inside layer of the blister cavity or the capsule material that is in contact with the dry powder formulation is an antistatic material according to the present invention can be used in the treatment of several respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD) and allergic rhinitis. Accordingly, these respiratory diseases can be, but not limited to, allergic and non-allergic asthma at any phases, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), intensifying of airways hyperactivity, bronchiectasis, chronic obstructive pulmonary, airways or lung disease including amphizem and chronic bronchitis, pneumokoniosis, aluminosis, antracosis, asbetosis, calicosis, phytilosis, ciderosis, silicosis, tabacosis, bissnosizn. This treatment can be prophylactic or symptomatic. In addition, said composition is preferably used for symptomatic treatment of asthma, COPD and allergic rhinitis.

A method for preparing the pharmaceutical composition according to the present invention comprises micronizing the formoterol fumarate and mometasone froate, preferably by air jet mill, mixing micronized formoterol fumarate and mometasone froate with lactose and blending the composition to obtain a homogeneous dry powder mixture and then filling the obtained dry powder mixture into capsules or blisters.

The pharmaceutical composition pertaining to the present invention can be explained with, but not limited to, the examples given below.

EXAMPLE 1

The dry powder formulation which is appropriate for a gelatine capsule used in the capsule inhalator comprises 18 parts of formoterol fumarate which was micronized in air jet mill and which has a mean particle size of 1,5 to 4.5 μm; 200 parts of mometasone froate which was micronized in air jet mill and has a mean particle size of 1.5 to 4.5 μm, and 4500 parts of lactose as carrier which has a mean particle size below 100μm.

Formoterol fumarate given in this example comprises its all pharmaceutically acceptable solvates, polymorphs, amorphous forms and crystalline forms. Mometasone froate given in this example comprises its all pharmaceutically acceptable solvates, hydrates and/or enantiomers, polymorphs, amorphous and crystal forms. Lactose, which is used as carrier, can optionally be added in a higher or a lower amount. The capsule described in the example is made up of gelatine and it can optionally be made of chitosan, starch and/or starch derivatives, cellulose and/or cellulose derivatives or synthetic polymers and the inside layer of the blister cavity or the capsule material that is in contact with the dry powder formulation is an antistatic material. The amounts given in the table below can be replaced with the amounts given in example 1:

Example	Amount of formoterol fumarate (parts)	Amount of mometasone froate (parts)	Amount of lactose (parts)
2	9	200	4000
3	9	200	5000
4	9	200	4500
5	18	400	5500
6	18	400	5000
7	18	400	6000
8	18	200	4000
9	18	400	6000
10	9	200	5750
11	9	200	4750
12	9	200	4200
13	9	200	5200
14	9	400	5500
15	18	200	4600
16	18	400	4800
17	9	400	6000
18	9	400	6000
19	18	400	4750

EXAMPLE 20

A dry powder formulation which is suitable to be stored in blisters so as to be used in a multiple dosing inhalator comprises 18 parts of formoterol fumarate which has an average particle diameter of 1.5-4.5 μm and was micronized in air jet mill; 200 parts of mometasone froate which was micronized in air jet mill, and 1000 parts of lactose having a particle diameter of less than 100 μm as a carrier.

Formoterol fumarate given in this example comprises its all pharmaceutically acceptable solvates, polymorphs, amorphous forms and crystalline forms. Mometasone froate given in this example comprises its all pharmaceutically acceptable solvates, hydrates and/or

enantiomers, polymorphs, amorphous and crystal forms. Lactose, which is used as carrier, can optionally be added in a higher or a lower amount.

The example can be repeated by replacing the amounts in Example 20 with the amounts given in the table below.

SAMPLE	Amount of formoterol fumarate (parts)	Amount of mometasone froate (parts)	Amount of lactose (parts)
21	9	200	11000
22	18	200	12000
23	18	200	14000
24	9	200	15000
25	9	200	13000
26	18	200	12500
27	9	400	15000
28	9	400	15500
29	18	400	12000
30	9	200	12500
31	9	200	16000
32	18	400	17000
33	9	400	16750
34	9	400	12500
35	18	200	13500
36	9	400	14500
37	9	400	17000
38	18	400	16500

CLAIMS

1. A medicament composition in dry powder form characterized in that said dry powder medicament composition comprises formoterol fumarate and mometasone froate wherein;
   - the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
   - said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
   - lactose which has s mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier and said composition is stored in capsules or blisters wherein the inside layer of the blister cavity or the capsule material that is in contact with the dry powder formulation is an antistatic material.
2. The medicament composition in dry powder form according to claim 1, wherein formoterol fumarate comprises its pharmaceutically acceptable solvates, polymorphs, crystal forms and amorphous forms and/or combinations thereof.
3. The medicament composition in dry powder form according to claim 1, wherein mometasone froate comprises its pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, polymorphs, crystal forms and amorphous forms and/or combinations thereof.
4. The medicament composition in dry powder form according to claim 2, wherein the amount of formoterol fumarate is in the range of 1 to 30μg.
5. The medicament composition in dry powder form according to claim 3, wherein the amount of mometasone froate and/or pharmaceutically acceptable derivatives of its is in the range of 50 to 600 μg.
6. The medicament composition in dry powder form according to claim 1, wherein lactose which has a mean particle size less than 100 μm is used as a mixture of particles which has two different mean particle sizes.
7. The medicament composition in dry powder form according to claim 6, wherein lactose which has a mean particle size less than 100 μm present as a mixture of particles having a mean particle size less than 10 μm and particles having a mean particle size in the range of 10 μm to 100 μm.

8. The medicament composition in dry powder form according to claim 7, wherein the fine lactose particles have a mean particle size between 2 μm and 8μm and the coarse lactose particles have a mean particle size between 30 μm and 80 μm.
9. The medicament composition in dry powder form according to claim 7, wherein the ratio between the fine lactose particles which have a mean particle size less than 10 μm and the coarse lactose particles which have a mean particle size in the range of 10 μm to 100 μm is in the range of 20:80% and 40:60% by weight.
10. The medicament composition in dry powder form according to claim 1, wherein the amount of lactose is in the range of 0.1-50 mg.
11. The medicament composition in dry powder form according to claim 1, wherein the antistatic material used is antistatic itself or it is not antistatic itself but contains antistatic agent(s).
12. The medicament composition in dry powder form according to claim 11, wherein the antistatic agents used are selected from a group comprising long-chain aliphatic amines (optionally ethoxylated) and amides, glycerol monostearate (GMS), saturated fatty acids, (poly)unsaturated fatty acids, quaternary ammonium salts (e.g., behentrimonium chloride or cocamidopropyl betaine), sulfonated organic compounds, esters of phosphoric acid, polyethylene glycol esters, or polyols and combinations thereof.
13. The medicament composition in dry powder form according to claim 1, wherein said composition in dry powder form can be stored in blister packs.
14. The blister pack according to claim 13, wherein each blister cavity constituting the blister pack contains at least one dose.
15. The blister pack according to claim 13, wherein the cavity volume of the blister is in the range of 17-30 mm^3.
16. The blister pack according to any of the claims 14 and 15, wherein the blister cavity is filled up to 25-100% of the total volume.
17. The medicament composition in dry powder form according to claim 1, wherein said pharmaceutical composition in dry powder form can be stored in capsules.
18. The capsule according to claim 17, wherein said capsule is made of a material selected from a group consisting of gelatine, chitosan, starch and/or starch derivatives, cellulose and/or cellulose derivatives or synthetic polymers.
19. The capsule according to claim 17, wherein the capsule material can be selected from a group consisting of hydroxypropyl cellulose, hydroxypropylmethyl cellulose, methyl

cellulose, hydroxymethyl cellulose,hydroxy ethyl cellulose, in the case that said capsule is made of cellulose or cellulose derivatives.

20. The capsule according to claim 17, wherein the capsule material can be selected from a group consisting of polyethylene, polyester, polyethyleneterephythalate, polycarbonate or polypropylene, in the case that said capsule is made of synthetic polymer.
21. The capsule according to claim 17, wherein polyethylene glycol, sorbitol, glycerol, propylene glycol, polyethylene oxide, polypropylene oxide block copolymer and/or other polyalcohols and polyether which have various molecular weights can be added into the capsule as adjuvant, in the case that said capsule is made of gelatin.
22. The capsule package according to claim 17, wherein the moisture rate is in the range of 10 to 20%, preferably 15 to 20%.
23. The capsule package according to claim 17, wherein the volume of said capsule pack is in the range of 0.1 to 0.52 ml.
24. The capsule package according to claim 17, wherein the capsule cavity is filled up to 0.01 to 25% of the total volume.
25. The medicament composition in dry powder form comprising formoterol fumarate and mometasone froate wherein;

- the mean particle size of formoterol fumarate and mometasone froate is in the range of 1.5 to 4.5 μm and
- said active agents are present in the composition with the ratio of 1:15 to 1:95 respectively and
- lactose which has a mean particle size less than 100 μm and total water content in the range of 4%-6% is used as carrier and said composition is stored in capsules or blisters wherein the inside layer of the blister cavity or the capsule material that is in contact with the dry powder formulation is an antistatic material for use in treatment of respiratory diseases especially asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD)

İSTEMLER

1. Formoterol ve mometazon ve/veya bunların farmasötik olarak türevlerini içeren bir farmasötik bileşim olup özelliği, farmasötik bileşimi oluşturan bileşenlerin kuru toz formunda bulunmasıdır.

2. İstem 1'e göre kuru toz formundaki bir farmasötik bileşim olup özelliği, iki aktif maddenin bir arada olması ve şerit şeklindeki katmanlarına ayrılabilir alüminyum blister ambalajda depolanmasıdır.

3. Istem 1 ve 2'ye uygun bir farmasötik bileşim olup özelliği, ilacın hastaya kuru toz alımına uygun bir cihaz ile verilmesidir.

4. İstem 1'e göre bir farmasötik bileşim olup özelliği içerdiği formoterolün, farmasötik olarak kabul edilebilir hidratları, solvatları, esterleri, enantiomerleri, polimorfları, tuzları, kristal ve amorf formları, tuzları veya serbest baz formunda ve/veya bunların kombinasyonu halinde bulunabilmesidir.

5. İstem 1'e göre bir farmasötik bileşim olup özelliği içerdiği mometazonun, farmasötik olarak kabul edilebilir hidratları, solvatları, esterleri, enantiomerleri, polimorflar, tuzları, kristal ve amorf formunda veya serbest baz formunda ve/veya bunların kombinasyonu halinde bulunabilmesidir.

6. Istem 1'e göre bir farmasötik bileşim olup özelliği bahsedilen kombinasyonu oluşturan aktif maddelerin yeterli miktarları ile birlikte isteğe bağlı olarak farmasötik olarak uygun bir ya da daha fazla taşıyıcı madde içermesidir.

7. Istem 6'ya göre bir taşıyıcı madde olup özelliği monosakkarit, disakkarit, polisakkarit ve oligosakkaritlerden oluşan gruptan seçilmesidir.

8. Önceki istemlerden birine göre bir farmasötik bileşim olup özelliği içerdiği taşıyıcı miktarının 0-50mg aralığında olmasıdır.

9. İstem 1'e göre kuru toz formunda bir farmasötik bileşim olup özelliği ihtiva ettiği aktif maddelerin ortalama partikül çapının 20μm'den daha küçük olmasıdır.

10. Önceki istemlerden birine göre bir farmasötik bileşim olup özelliği ihtiva ettiği mometazon ya da farmasötik olarak uygun bir türevinin formoterol ya da farmasötik olarak uygun bir türevine ağırlıkça oranı 1:1 ila 100:1 aralığında, tercihen 1:1 ila 80:1 aralığında olmasıdır.

11. Istem 2'ye göre şerit şeklindeki katmanlarına ayrılabilir blister ambalaj olup her bir blisterin ihtiva ettiği kuru toz formunda bir farmasötik bileşim olup özelliği mometazon içeriğinin 1-700µg aralığında, formoterol içeriğinin 1-50µg aralığında olmasıdır.

12. İstem 2'ye göre şerit şeklindeki katmanlarına ayrılabilir blister ambalaj olup özelliği içerdiği blisterlerin kavite hacminin 17 ila 30mm^3, tercihen 18 ila 23mm^3, özellikle tercihen 19 ila 21mm^3 arasında olmasıdır.

13. Istem 2'ye göre şerit şeklindeki katmanlarına ayrılabilir blister ambalaj olup, özelliği inhalasyon işleminden önce birbirinden ayrılarak açılan alt ve üst katmanlardan oluşmasıdır.

14. Istem 13'ye göre şerit şeklindeki katmanlarına ayrılabilir blister ambalajın alt katmanı olup, özelliği polimerik tabaka ve alüminyum folyoyu da içeren birden fazla tabakadan oluşabilmesidir.

15. Istem 13'ye göre şerit şeklindeki katmanlarına ayrılabilir blister ambalajın üst katmanı olup özelliği polimerik tabaka ve alüminyum folyoyu da içeren birden fazla tabakadan oluşabilmesidir.

16. Istem 13 ila 15'den herhangi birinde bahsedilen şerit şeklindeki katmanlarına ayrılabilir blister ambalajı oluşturan katmanların içerdiği polimerik tabaka olup özelliği tercihen desikant içermesidir.

17. İstem 16'da bahsedilen şerit şeklindeki katmanlarına ayrılabilir blister ambalajı oluşturan katmanların polimerik tabakaları olup özelliği polimerik maddenin tercihen termoplastiklerden veya diğer sentetik polimerlerden seçilmesidir.

18. Istem 1'e göre bir farmasötik bileşim olup özelliği kronik obstrüktif akciğer hastalığı (KOAH), alerjik rinit, her aşamadaki alerjik olan ya da olmayan astım hastalığı, akut akciğer hasarı (ALI), havayolları hiperaktivitesinin şiddetlenmesi, bronşiektaz, amfizem, kronik bronşiti içeren kronik obstrüktif akciğer, solunum yolu ya da akciğer hastalığı (COPD, COAD, ya da COLD), pnömokoniosiz, aluminosiz, antrakosiz, asbetosiz, kalikosiz, ptilosiz, siderosiz, silikosiz, tabakosiz ve bissnosizin'in profliaktik ve/veya semptomatik tedavisinde kullanılmasıdır.

19. Istem 18'e göre bir farmasötik bileşim olup özelliği tercihen alerjik rinit, KOAH ve astımın semptomatik tedavisinde kullanılmasıdır.