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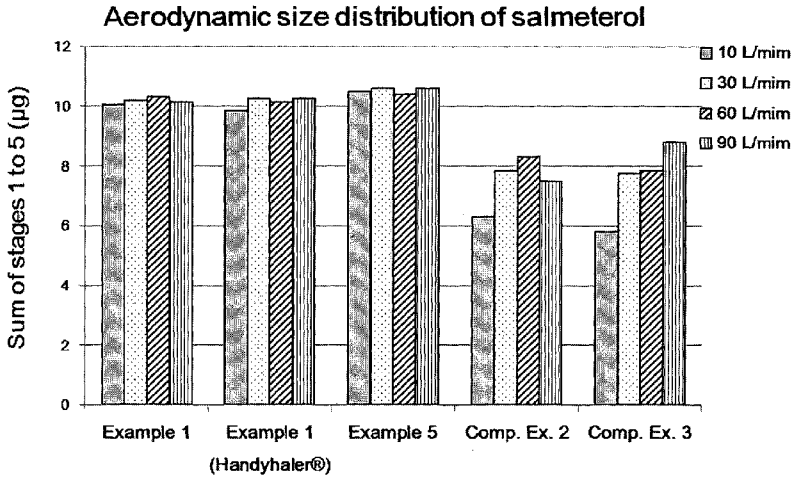
(54) Title: DRY POWDER FOR INHALATION FORMULATION COMPRISING SALMETEROL XINAFOATE, FLUTICASONE PROPIONATE AND TIOTROPIUM BROMIDE, AND METHOD FOR PREPARING SAME



(57) Abstract: Provided is a dry powder for inhalation formulation comprising salmeterol xinafoate, fluticasone propionate and tiotropium bromide, as pharmaceutically active ingredients, and a carrier, and an inhalation formulation comprising same. The inventive dry powder inhalation formulation having good content uniformity and showing small changes in the aerodynamic size distribution in accordance with the flow rate changes can effectively deliver said pharmaceutically active ingredients to a target site upon administration, and thus can be useful in the prevention or treatment of respiratory diseases, particularly asthma and COPD.

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DESCRIPTION
DRY POWDER FOR INHALATION FORMULATION COMPRISING SALMETEROL XINAFOATE, FLUTICASONE PROPIONATE AND TIOTROPIUM BROMIDE, AND METHOD FOR PREPARING SAME

FIELD OF THE INVENTION

The present invention relates to a dry powder for inhalation formulation comprising salmeterol xinafoate, fluticasone propionate and tiotropium bromide, and method for preparing same.

BACKGROUND OF THE INVENTION

Various medicaments have been used in the form of inhalation formulation for the treatment of respiratory diseases, e.g., asthma and chronic obstructive pulmonary disease (COPD). A particular advantage of inhalation formulation is that only a small amount of a pharmaceutically active ingredient is required to achieve the desired therapeutic effect; however, there are drawbacks to the formulation that only a part of the pharmaceutically active ingredient administered will be delivered to a target site, or there is a great possibility that the pharmaceutically active ingredient will be delivered to sites where no treatment is required, thereby causing adverse side effects. Thus, continuous efforts are being made to maximize the therapeutic effect of the formulation so as to achieve reliable targeted delivery to the site where the therapeutic effect is desired and to prevent the delivery of the pharmaceutically active ingredient to the site where no treatment is required.

For effective administration of inhalation formulation, inhalers, which administer the drug by sucking in the air with the drug and delivering them into the air passage, have been widely used for treatment of respiratory diseases. The most common inhaler systems are metered dose inhalers (MDI), which had been used extensively since its approval in 1956, and once occupied 80% of the inhaler market. However, a rise of environmental concerns, e.g., depletion of ozone layer and global

warming, has shifted research interests to focus on dry powder inhalers (DPI) in recent years. In current stage, researchers are concentrating their efforts to remedy the shortcomings of MDI formulations by employing DPI formulations. MDIs typically comprise pharmaceutically active ingredients and a solvent as a propellant in compressed state, which deteriorates its stability; and the spraying speed is fast, and thus it reaches laryngopharyngeal space too fast. DPIs, however, are easy to use; and only comprised of powder solid particles, and therefore are advantageous in terms of stability (*see* Martin J Telko and Anthony J Hickey, Dry Powder Inhaler Formulation, Respiratory Care, September 2005, Vol 50, No. 9).

Meanwhile, various drugs are being tested for the prevention and treatment of respiratory diseases. For example, a selective beta-2 adrenoceptor agonist (beta-2 agonist) can induce bronchodilation, and can be used to relieve respiratory distress. Beta-2 agonists may be broadly divided into short-acting beta-2 agonists and long-acting beta-2 agonists. Short-acting beta-2 agonists, e.g., salbutamol, fenoterol, levalbuterol, terbutaline, etc., provide immediate relief, but their reaction time is rather short. In contrary, long-acting beta-2 agonists, e.g., formoterol, indacaterol, salmeterol, tulobuterol, etc., provide sustained bronchodilation, but patients are required to take them two or more times per day because the normal reaction time of these drugs is less than 12 hours.

Beta-2 agonists can alleviate bronchoconstriction in patients, but other drugs, e.g., steroids, are used to treat inflammation, which is another cause of asthma. Examples of steroids include inhaled corticosteroid (ICS) such as beclomethasone, budesonide, flunisolide, fluticasone propionate, mometasone furoate, triamcinolone, and the like.

Also, another type of drugs called an inhaled anticholinergic is well-known as a stable and effective bronchodilator which can be used for treatment of COPD. Anticholinergic agents can increase the level of forced expiratory volume in 1 second (FEV1), prevent static or dynamic hyperinflation (overexpanded lung), and reduces exacerbations of COPD. There is a limited number of inhaled anticholinergic bronchodilators that are currently available, e.g., rapid-onset types such as ipratropium bromide, oxitropium bromide, etc., and long-acting types such as tiotropium bromide, etc.

Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) are suggesting an incremental treatment method based on the progression of the disease condition, which includes the use of a combination formulation of drugs having different or complementary action mechanisms. For instance, a long-acting beta-2 agonist is prescribed to patients with asthma or COPD having FEV1 level of less than 80%, and COPD patients with accompanying respiratory distress having FEV1 level of less than 50% or who are experiencing frequent acute exacerbations are prescribed with ICS in addition to beta-2 agonists.

A number of combinations of the aforementioned drugs are known already, and one typical example is an inhalation formulation comprising salmeterol xinafoate and fluticasone propionate (Seretide, GSK). Currently, Seretide is available in MDI (Evohaler) and DPI (Diskus) formulations. Seretide provides an effective bronchodilation induced by the long-acting beta-2 agonist salmeterol, as well as potent anti-inflammatory action caused by the ICS, fluticasone propionate. In case of Seretide Diskus formulation, which is provided in the form of DPI formulation, both beta-2 agonist and inhaled corticosteroid may be inhaled at once, but the formulation does not show sustained bronchodilation action, and thus patients are required to take the formulation two or more times per day. Another drawback of this formulation lies in that the amount of the excipient is too small to give a sensation in the lungs upon administration, and sometimes the dose is not properly delivered or is taken two or more times because it is impossible to observe administered formulation.

Also, a combination therapy comprising a rapid-onset anticholinergics ipratropium bromide and a long-acting beta-2 agonist salmeterol is disclosed in WO01/76601, and an additional combination therapy using anticholinergics, beta-2 agonist as well as steroid is disclosed in U.S. Pat. No. 6,423,298 and WO02/7672.

Nevertheless, said formulations do not relate to a triple combination formulation which can exert fast-acting bronchodilation induced by a beta-2 agonist, anti-inflammatory action by a corticosteroid, and sustained bronchodilation by an anticholinergic at once.

Recently, KR Patent Laid-Open Publication Nos. 10-2010-0063116 and 10-2009-0121338 mentioned about a triple combination formulation of beta-2 agonist, corticosteroid, and anticholinergic. However, they neither consider any specific

device, effective dose amount, manufacturing method thereof, packaging type, particle size of the carrier material, etc., nor provide assessment data thereof. Pressure drop values of inhalation formulations, especially in the form of dry powder inhalation formulations, vary when different types of devices are used, and the amount of active ingredient delivered to lungs may vary with packaging forms, e.g., blister packaging vs. capsule packaging. Properties and ratio of excipient (such as lactose, etc.), which is used as a carrier, can also cause a large difference in therapeutic effects. Moreover, even if drugs from the same drug group were used, undesirable results such as deterioration in uniformity and storage stability may occur depending on physicochemical properties of the respective drugs.

Although some drugs and a combination formulation thereof for the prevention or treatment of respiratory diseases are known, there are no specific compositions or preparation method thereof developed for a triple combination formulation which can administer a long-acting beta-2 agonist, an inhaled corticosteroid and an anticholinergic together at once. Thus, there has been a need to develop a composition of a composite formulation, which can stably and accurately administer said three groups of drug in a single dose, to improve patient compliance and enhance patients' convenience to carry the formulation.

SUMMARY OF THE INVENTION

Therefore, it is an object of the present invention to provide a dry powder for inhalation formulation comprising salmeterol xinafoate, fluticasone propionate and tiotropium bromide, having good content uniformity and showing small changes in the aerodynamic size distribution in accordance with the flow rate changes, which can effectively deliver said pharmaceutically active ingredients to a target site upon administration.

It is another object of the present invention to provide an inhalation formulation comprising the dry powder.

It is still another object of the present invention to provide a method for preparing the dry powder for inhalation formulation.

In accordance with one object of the present invention, there is provided a dry powder for inhalation formulation comprising salmeterol xinafoate, fluticasone propionate, tiotropium bromide, and a carrier, having an average particle size in a range of 30 to 120 μm.

In accordance with another object of the present invention, there is provided an inhalation formulation comprising the dry powder for inhalation formulation.

In accordance with still another object of the present invention, there is provided a method for preparing the dry powder for inhalation formulation, which comprises the steps of: (1) applying 5 to 20 wt% of a carrier, based on the total amount of the carrier, onto inner walls of a mixer; (2) triturating salmeterol xinafoate, fluticasone propionate and tiotropium bromide with 5 to 20 wt% of the carrier, based on the total amount of the carrier; and (3) placing the triturated ingredients and the remaining carrier in the mixer prepared in Step (1), and then pulverizing the mixture with a force not sufficient to substantially alter the size of the particles, followed by admixing.

The dry powder for inhalation formulation according to the present invention having good content uniformity and small changes in the aerodynamic size distribution in accordance with the flow rate changes can deliver said three active ingredients together upon administration, thereby enhancing patients' convenience to carry the formulation as well as improving patient compliance, and thus have good therapeutic compliance in the treatment of respiratory diseases, particularly in asthma and COPD.

BRIEF DESCRIPTION OF DRAWINGS

Fig. 1 shows the analysis of the aerodynamic size distribution of salmeterol in accordance with Test Example 2.

Fig. 2 shows the analysis of the aerodynamic size distribution of fluticasone in accordance with Test Example 2.

Fig. 3 shows the analysis of aerodynamic size distribution of tiotropium in accordance with Test Example 2.

DETAILED DESCRIPTION OF THE INVENTION

The dry powder for inhalation formulation in accordance with the present invention comprises, as active ingredients, salmeterol xinafoate as a long-acting beta-2 agonist, fluticasone propionate as an inhaled corticosteroid, and tiotropium bromide as an anticholinergic agent, and additionally a carrier, having an average particle size in a range of 30 to 120 μm.

In the present invention, specific salts or solvates of each active ingredient were employed; however, those skilled in the art may employ any equivalents having the same or similar activities in lieu of the specific salts or solvates. Examples of the equivalents include pharmaceutically acceptable salts, solvates, hydrates, enantiomers, derivatives, polymorphs, and prodrugs thereof, but not limited thereto.

In order to effectively deliver the pharmaceutically active ingredients to a lung to exert pharmacological activity, particles of each active ingredient must be micronized. Generally, the size of a particle which is suitable to be administered by inhalation is greater than 0.1 μm and less than or equal to 10 μm, preferably greater than 0.1 μm and less than or equal to 5 μm. If the size of the particle is 0.1 μm or smaller, the particles may be discharged from the body, rather than being absorbed by the bronchial tube. Hence, according to USP 34 <601> 'Aerosol, Nasal spray, Metered-dose inhaler and Dry powder inhaler,' various equipments, e.g., Apparatus 1~6, are suggested to measure the aerodynamic size distribution for MDI and DPI formulations. For example, one can determine that the main ingredient collected during stages 1~5 has the aerodynamic size distribution in a range of 0.1 to 5 μm when using Apparatus 3 (Anderson Cascade Impactor) of USP 34 <601>, which allows prediction of the effective amount which can exert pharmacological activity upon administration of inhalation formulation by measuring the amount. Generally, the particle size distribution which covers this area is preferably 10 to 30% of the active ingredient content measured for inhalation.

However, small particles are thermodynamically unstable due to their high surface area to volume ratio, and an excessive surface free energy may cause particles to agglomerate easily. When the particles agglomerate, they are attached to the capsule or the inner wall of the inhalation device to interrupt the release of the powder.

Therefore, pharmaceutically acceptable excipients, i.e., carrier particles, may be employed so as to redress such problems.

Specifically, it is preferred that micronized pharmaceutically active ingredients are attached to carrier particles to yield thermodynamic stability, prevent agglomeration, and thus effectively transport the particles inside the body upon inhalation. Also, the pharmaceutically active ingredients should be easily discharged from the surface of the carrier particles in the respiratory tract to reach target sites once administered. Generally, the size of carrier particles is considerably large so that they cannot reach target sites directly, and thus, if the active ingredients are not easily discharged from the carrier, the amount of the pharmaceutically active ingredients that can reach target sites would significantly decrease. Meanwhile, the flowability of the carrier particle increases with the size of the particle, therefore the size of the carrier should be large enough to transport the particle out of the inhalation device easily.

Accordingly, the size of the carrier used in the dry powder for an inhalation formulation must be suitable to yield good flowability. In one embodiment, the size of the carrier particle is 30 to 120 μm. Such carrier particle may be mixed with micronized carriers to allow uniform attachment of the pharmaceutically active ingredient particles to the carrier particles and also make it easy to discharge the pharmaceutically active ingredient particles from the carrier particles in the respiratory tract. In general, this can be accomplished by attaching a small amount of micronized carrier particles primarily to the irregular surface of the carrier particles, so that the micronized carrier particles are attached to the surface with a high surface energy first to lower the surface energy thereof, lowering overall surface energy and allowing the carrier particles to have homogeneous distribution of surface energy. The average diameter of the micronized carrier particles may be 35 μm or less, preferably 30 μm or less, more preferably 25 μm or less. Further, the micronized carrier particles may be used in such an amount that the flowability of the inhalation composition will not be affected, e.g., 0.1 to 20 wt% based on the total weight of carrier particles. In an embodiment, the micronized carrier particle may be used in an amount of 1 to 15 wt%, and in another embodiment, the micronized carrier particle may be used in an amount of 3 to 12 wt%. Generally, micronized carrier particles may be mixed with carrier particles; alternatively, commercially available carrier particles with uniform size may be employed in the present invention.

Also, the surface properties of the carrier particles are important factors which affect the discharge of the pharmaceutically active ingredients from the inhalation device or the delivery of the active ingredients to the target sites. The pharmaceutically active ingredients are required to have enough adhesion force with the surface of the carrier particles to allow good flowability so that they can be easily discharged from the inhalation device; at the same time, the pharmaceutically active ingredients must be easily discharged from the surface of the carrier in the respiratory tract so as to reach the target sites once it leaves the inhalation device, and thus there is a difficulty in maintaining an appropriate adhesion force between the surface of the carrier and the pharmaceutically active ingredients. In the present invention, the pharmaceutically active ingredients and the carriers are subjected to a soft pulverization and a mixing process, to yield a suitable adhesion force between them.

Selecting an excipient as a carrier is an important factor in the composition of an inhalation formulation, particularly a composite inhalation formulation comprising two or more of pharmaceutically active ingredients. Examples of the excipient employable for the present invention include monosaccharides such as glucose, arabinose; disaccharides such as lactose, maltose, sucrose; polysaccharides such as starch, dextrin or dextran; polyalcohols such as sorbitol, mannitol, and xylitol; and hydrates thereof. In an embodiment of the present invention, monosaccharides or disaccharides are employed as an excipient; in another embodiment of the present invention, lactose is employed; and in still another embodiment of the present invention, lactose monohydrate is used.

Selecting an appropriate amount of the carrier is also important. An excessive amount of the carrier in the formulation not only causes patients to feel unpleasant due to excessive foreign body sensation, but also could cause asthma due to the carrier, a foreign body. Moreover, if the amount employed is too small, it becomes difficult to obtain uniformity between the carrier and the pharmaceutically active ingredients, and to measure one dose in a capsule or a blister packaging. Thus, in the present invention, the amount of the carrier employed is in a range of 15 mg to 25 mg. Said amount can be charged in a capsule or a blister packaging by conventional methods which do not requires any special equipment, giving the advantage that the formulation can be manufactured in conventional pharmaceutical manufacturing facilities without any modification.

In the inhalation formulations, however, the amount of the pharmaceutically active ingredient is very small as compared to the amount of the carrier. Since a conventional simple mixing may cause a difficulty in procuring the content uniformity, other methods such as trituration may be used to mix the active ingredient with the carrier so as to resolve such problem. Trituration refers to a method in which pharmaceutically active ingredients and excipients are mixed in a ratio of 1:1 to 1:4, e.g., 1:1, 1:2, or 1:4, and the excipients are added in the same ratio to the mixture prepared repeatedly until all the excipients are used up. Nevertheless, in the case of the inhalation formulations comprising pharmaceutically active ingredients with very small particle size which also take up relatively a very small portion of the total contents, there may be a problem with the content uniformity even by the trituration process.

Accordingly, a layered mixing process using a screening device was employed to maintain content uniformity as disclosed in KR Pat. No. 0849837. In this process, big and small particles, however, must be separated before using the process, and each of ten or more, preferably 30 or more, fractions are required to pass through the screening device, thereby causing a great inconvenience.

Therefore, the present inventors have endeavored to redress said problems and have discovered that subjecting the pharmaceutically active ingredients and the carriers to a soft pulverization and a mixing process could resolve the problem in the content uniformity of the inventive inhalation formulation. The term 'soft pulverization and mixing' as used herein, refers to the process of placing a powder in a blender equipped with a ball or chopper followed by mixing, wherein the pulverization is conducted by rotating the blender and the particles of the powder are pulverized by the ball or chopper with a force not sufficient to substantially alter the size of the particles, e.g., to a degree of less than 20% of the size change. The size of the carrier particles gets smaller when they are exposed to a strong physical force for a long period of time. If the size of the carrier particles is too small, then flowability of the powder deteriorates and the powder may remain in the inhalation device or the capsule, thereby causing a difficulty in delivering desirable amount of the pharmaceutically active ingredient to the target sites. In a preferred embodiment, the dry powder for inhalation formulation of the present invention has an average particle size in a range of 30 to 120 μm. If the average particle size is in the said range, the content uniformity of the

pharmaceutically active ingredient is satisfactory and the particle size distribution does not fluctuate with the change in flow rate. However, if the average particle size exceeds 120 μm, the content uniformity deteriorates and causes the pharmaceutically active ingredients to remain in the inhalation device or the capsule when the formulation is inhaled. Also, if the average particle size is less than 30 μm, the effective amount of the pharmaceutically active ingredients is heavily changed depending on flow rate. In another preferred embodiment, the dry powder for inhalation formulation of the present invention has an average particle size in a range of 55 to 65 μm.

In the mixing process, a small amount of carrier is applied on the chopper and the walls of the blender, and then a certain amount of the carrier and the pharmaceutically active ingredients are triturated and sieved, followed by soft pulverization and mixing. Preferably, the amount of the carrier to be applied on the chopper and the walls is in a range of 5 to 20 wt%, based on the total amount of the carrier; and the amount of the carrier to be triturated with the pharmaceutically active ingredient is in a range of 5 to 20 wt%, based on the total amount of the carrier, but not limited thereto. The pharmaceutically active ingredients have very small sized particles and a high surface energy which gives them a sticky property, so there is a high possibility of loss in active ingredients if they were placed first in the blender because they could stick to the chopper and the walls of blender. Thus, this can be prevented by applying a suitable amount of the carrier having a good flowability onto the chopper and the walls of the blender. Next, the pharmaceutically active ingredients and the carrier are triturated and sieved, followed by a soft pulverization and a mixing process. Preferably, the mixing process is carried out at a relative humidity of 40 to 60%. If the relative humidity is too low, it becomes difficult to carry out the mixing process due to static electricity; and even if the mixing process is carried out successfully, there is a high chance of losing a large amount of the particles during the process. Also, if the relative humidity is too high, the particles have a tendency to absorb moisture and to form agglomerates. Due to its hygroscopic properties, the stability of salmeterol xinafoate, in particular, cannot be secured if it is exposed to an excessive amount of moisture during a long-term storage.

As explained above, the present invention provides a method for preparing the dry powder for inhalation formulation, which comprises the steps of: (1) applying 5 to

20 wt% of the carrier, based on the total amount of the carrier, on inner walls of a mixer; (2) triturating salmeterol xinafoate, fluticasone propionate and tiotropium bromide with 5 to 20 wt% of the carrier, based on the total amount of the carrier; and (3) placing the triturated ingredients and the remaining carrier in the mixer prepared in Step (1), and then pulverizing the mixture with a force not sufficient to substantially alter the size of the particles, followed by admixing.

Meanwhile, the present invention provides an inhalation formulation comprising the dry powder contained in the form of a capsule and a cartridge comprising gelatin or hypromellose, or a blister pack comprising a plurality of aluminum thin layers, preferably in the form of a capsule. The capsule size of the inventive formulation is preferably No. 1 to No. 4. In one embodiment of the present invention, the capsule size is No. 3. One of the advantages of preparing the formulation in the form of the capsule is that it can be manufactured without requiring any special equipment. Also, the capsule, which is charged with the composition of the present invention, is preferably made of a transparent material. If the inventive formulation is provided in a transparent capsule, patients can check whether or not they have taken the required medication properly after they were administered with the inventive formulation with their own eyes. Also, the patients can check for product defects or deterioration of the quality in the dry powder such as agglomeration or discoloration with their eyes before they take the formulation.

The device used for administration of the dry powder refers to a device which breaks, punches or uses any other method to open the capsule to allow delivery of the weighed compositions to the lung of a patient. Also, the device may further comprise an air inlet which creates an air flow where air enters the device, an air outlet which discharges the pharmaceutically active ingredients when patients inhale the air, and a particulate filter to filter any impurities. Examples of such devices that are currently available in the market include ROTAHALER® (GSK), HANDIHALER® (Boehringer Ingelheim), and AEROLIZER® (PLASTIAPE). The inhalation formulation in accordance with the present invention may be used with any device which can utilize a capsule composition, preferably AEROLIZER®. In the device, there is a hole in the center of the device to place a capsule and when the buttons on the sides are pressed, pins come out to punch holes to make ready for the administration of the formulation. The device is relatively small, and hence has good portability.

In the DPI inhalation device as described above, the driving force which takes in the pharmaceutically active ingredients from the capsule is the inhalation force of the patient. All DPI devices have the pressure drop value which is induced by airflow when the patient is administered with the formulation, and the pressure drop values which vary with the airflow can be the important variable in aerodynamic size distribution and content uniformity tests for evaluation of the effective amount suitable for the inhalation formulation. In fact, peak inspiratory flow value will differ, e.g., from 10 to 100 L/min, depending on the type of device used, age of the patient and condition of the disease. The United State Pharmacopoeia suggests that a flow rate can be controlled from 0 to 100 L/min, and a flow rate that creates a pressure drop of 4 kPa across the inhaler (Q_{out}) and a suction time (T) obtained from the formula T(sec) = 240 / Q_{out} may be used to evaluate the tests results. Thus, it is preferable that the inventive formulation has small changes in the aerodynamic size distribution in accordance with the flow rate changes so as to give similar pharmaceutical effects among patients. The dry powder inhalation formulation in accordance with the present invention has an advantage that the aerodynamic size distribution of three pharmaceutically active ingredients does not fluctuate depending on the flow rate changes.

Therefore, the dry powder inhalation formulation in accordance with the present invention can effectively release the mixture from the inhalation device; easily discharge the pharmaceutically active ingredient from carrier in respiratory tract, thereby delivering the active ingredients to the target sites effectively; and show good content uniformity of pulverized pharmaceutically active ingredient and small changes in the aerodynamic size distribution in accordance with the flow rate changes.

In the dry powder inhalation formulation in accordance with the present invention, salmeterol xinafoate, fluticasone propionate and tiotropium bromide may be employed in amounts of 25 to 100 μg, 25 to 500 μg, and 5 to 50 μg, respectively, per dosage unit. However, employable amounts are not limited thereto, and may be adjusted depending on the various factors, e.g., the patient and disease condition being treated.

The dry powder inhalation formulation of the present invention comprising salmeterol, fluticasone and tiotropium can effectively control bronchoconstriction,

inflammation and secretion of the mucus in the respiratory tract, and thus can be useful in the treatment of respiratory diseases, particularly asthma and COPD.

Hereinafter, the present invention is described more specifically by the following examples, but these are provided only for illustration purposes, and the present invention is not limited thereto.

Example 1: Preparation of Dry Powder Inhalation Formulation I

2 mg of lactose is placed in a mixer to be applied onto the mixer. Salmeterol xinafoate, fluticasone propionate and tiotropium bromide in accordance with the compositions listed in Table 1, and 2 mg of lactose were triturated and placed in the mixer, and then the remaining lactose was placed in the mixer with balls, followed by admixing for 20 minutes. The mixture obtained was stabilized for 12 hours or more, and charged in a transparent size No. 3 capsule by using a capsule filling machine. The deviation of the contents charged in the capsules was satisfactory, which came out to be 3.4%, and the average particle size of the said composition was 60.19 μm as measured with a Sympatec HELOS laser diffraction sensor.

[Table 1]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.2500
Tiotropium bromide	0.0225 (tiotropium 0.018)
Lactose	20.0000
Total	20.3450

Example 2: Preparation of Dry Powder Inhalation Formulation II

The procedures of Example I were repeated, except for using tiotropium bromide in an amount of 0.01125 mg in accordance with Table 2 below, to obtain the dry powder inhalation formulation. The deviation of the contents charged in the

capsules was satisfactory, which came out to be 3.1%, and the average particle size of the said composition was 58.34 μm.

[Table 2]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.2500
Tiotropium bromide	0.01125 (tiotropium 0.009)
Lactose	20.0000
Total	20.33375

Example 3: Preparation of Dry Powder Inhalation Formulation III

The procedures of Example I were repeated, except for using fluticasone propionate in an amount of 0.5000 mg in accordance with Table 3 below, to obtain the dry powder inhalation formulation. The deviation of the contents charged in the capsules was satisfactory, which came out to be 4.5%, and the average particle size of the said composition was 56.91 μm.

[Table 3]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.5000
Tiotropium bromide	0.0225 (tiotropium 0.018)
Lactose	20.0000
Total	20.5950

Example 4: Preparation of Dry Powder Inhalation Formulation IV

The procedures of Example I were repeated, except for using fluticasone propionate in an amount of 0.1000 mg and tiotropium bromide in an amount of 0.01125 mg in accordance with Table 4 below, to obtain the dry powder inhalation formulation. The deviation of the contents charged in the capsules was satisfactory,

which came out to be 3.9%, and the average particle size of the said composition was 62.48 μm.

[Table 4]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.1000
Tiotropium bromide	0.01125 (tiotropium 0.009)
Lactose	20.0000
Total	20.18375

Example 5: Preparation of Dry Powder Inhalation Formulation V

The procedures of Example I were repeated, except for using lactose in an amount of 15 mg in accordance with Table 5 below, to obtain the dry powder inhalation formulation. The deviation of the contents charged in the capsules was satisfactory, which came out to be 4.8%, and the average particle size of the said composition was 63.57 μm.

[Table 5]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.2500
Tiotropium bromide	0.0225 (tiotropium 0.018)
Lactose	15.0000
Total	15.3450

Example 6: Preparation of Dry Powder Inhalation Formulation VI

The procedures of Example I were repeated, except for using lactose in an amount of 25 mg in accordance with Table 6 below, to obtain the dry powder inhalation formulation. The deviation of the contents charged in the capsules was satisfactory, which came out to be 3.2%, and the average particle size of the said

composition was 58.72 μm.

[Table 6]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.2500
Tiotropium bromide	0.0225 (tiotropium 0.018)
Lactose	25.0000
Total	25.3450

Comparative Example 1: Preparation of Dry Powder Inhalation Formulation VII

In accordance with Table 7 below, salmeterol xinafoate, fluticasone propionate, tiotropium bromide and lactose were placed in a mixer together, followed by admixing for 60 minutes. The mixture obtained was stabilized for 12 hours or more, and charged in a transparent size No. 3 capsule by using a capsule filling machine. The deviation of the contents charged in the capsules was satisfactory, which came out to be 4.9%, and the average particle size of said composition was 145.39 μm.

[Table 7]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.2500
Tiotropium bromide	0.0225 (tiotropium 0.018)
Lactose	20.0000
Total	20.3450

Comparative Example 2: Preparation of Dry Powder Inhalation Formulation VIII

The procedures of Comparative Example I were repeated, except for using lactose in an amount of 5 mg in accordance with Table 8 below, to obtain the dry

powder inhalation formulation. The average particle size of the said composition was 140.56 μm.

[Table 8]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.2500
Tiotropium bromide	0.0225 (tiotropium 0.018)
Lactose	5.0000
Total	5.3450

Comparative Example 3: Preparation of Dry Powder Inhalation Formulation IX

In accordance with the compositions listed in Table 9, the procedures of Example 1 was repeated using lactose, *i.e.*, Respitose® ML006 (DMV) having an average particle size of approximately 17 μm to prepare a mixture. The mixture obtained was stabilized for 12 hours or more, and charged in a transparent size No. 3 capsule by using a capsule filling machine. The deviation of the contents charged in the capsules was unsatisfactory, which came out to be 7.4%, and the average particle size of the said composition, measured by laser diffraction sensor HELOS (Sympatec) was 14.63 μm.

[Table 9]

Ingredient	(mg)
Salmeterol xinafoate	0.0725 (salmeterol 0.05)
Fluticasone propionate	0.2500
Tiotropium bromide	0.0225 (tiotropium 0.018)
Lactose	20.0000
Total	20.3450

Test Example 1: Evaluation of Content Uniformity

Capsule formulations obtained in Examples 1 and 2 and Comparative Example 1 were subjected to content uniformity evaluation of salmeterol, fluticasone and tiotropium under the following conditions. The results are shown in Tables 10 to 12. The acceptance value according to the results of individual content uniformity evaluation was calculated in accordance with the uniformity of dosage unit section in Korean Pharmacopoeia.

- Acceptance value =

$$|M - \bar{X}| + ks$$

M = reference value, X = mean of individual contents

k = acceptability constant (2.4 when n = 10), s = standard deviation

<Analytical conditions for salmeterol and fluticasone>

Column: stainless column (internal diameter of about 4.6 mm and length of 15 cm) packed with octadecylsilyl silica gel (diameter of 5 μm).

Mobile phase: methanol : acetonitrile : water = 50 : 16 : 34 (v/v/v) containing 0.6% (w/v) of ammonium acetate

Detector: UV-absorption detector (absorbance at 228 nm)

Column temperature: 40°C

Flow rate: 1.0 mL/min

Injection volume: 100 μL

<Analytical conditions for tiotropium>

Column: stainless column (internal diameter of about 4.6 mm and length of 15 cm) packed with octadecylsilyl silica gel (diameter of 5 μm).

Mobile phase: a mixed solution prepared by adding 300 mL of acetonitrile with 700 mL of a solution prepared by adding 1.79 g of sodium heptanesulfonate monohydrate in 1 L of water whose pH value was adjusted to 3.2 using a phosphoric acid

Detector: UV-absorption detector (absorbance at 240 nm)

Column temperature: 30°C

Flow rate: 2.0 mL/min

Injection volume: 10 μL

[Table 10] Content uniformity (%) of active ingredients in the dry powder inhalation formulation of Example 1

	Salmeterol (%)	Fluticasone (%)	Tiotropium (%)
1	96.2	102.6	96.2
2	94.6	96.7	96.8
3	94.9	103.7	99.3
4	103.2	94.6	101.0
5	96.8	92.6	99.0
6	104.6	98.5	101.7
7	99.0	103.1	99.0
8	106.2	96.6	97.4
9	102.6	103.6	99.9
10	102.5	103.9	100.9
Mean	100.1	99.6	99.1
S.D.	4.3	4.3	1.9
Acceptance Value	10.2	10.3	4.4

[Table 11] Content uniformity (%) of active ingredients in the dry powder inhalation formulation of Example 2

	Salmeterol (%)	Fluticasone (%)	Tiotropium (%)
1	96.4	100.2	99.4
2	98.7	100.5	99.1
3	98.6	100.7	101.3
4	96.4	99.6	101.5
5	100.8	96.9	96.1
6	98.6	100.6	100.6
7	100.8	100.0	98.4
8	100.8	100.7	101.5
9	100.9	100.6	101.4
10	96.5	98.5	92.9
Mean	98.9	99.8	99.2
S.D.	1.9	1.2	2.8

Acceptance Value	4.6	3.0	6.8

[Table 12] Content uniformity (%) of active ingredients in the dry powder inhalation formulation of Comparative Example 1

	Salmeterol (%)	Fluticasone (%)	Tiotropium (%)
1	92.3	88.6	101.6
2	88.5	110.7	112.2
3	120.6	112.6	88.7
4	95.6	98.7	89.4
5	98.6	87.6	105.7
6	92.4	92.4	110.7
7	85.6	120.4	92.7
8	110.8	88.7	86.9
9	106.7	92.4	93.4
10	98.6	98.6	105.5
Mean	99.0	99.1	98.7
S.D.	10.8	11.6	9.5
Acceptance Value	26.0	27.8	22.9

As shown in Tables 10 to 12 above, acceptance values of the three active ingredients in the dry powder inhalation formulations of Examples 1 and 2 were less than 15, ensuring the uniformity of the formulations. However, the acceptance values of the active ingredients in the dry powder inhalation formulation of Comparative Example 1 exceeded 20, and thus, showed inconsistency in the content uniformity.

Test Example 2: Aerodynamic Size Distribution of Active Ingredients

The aerodynamic size distribution of the dry powder inhalation formulation prepared in Examples 1 and 5, and Comparative Examples 2 and 3 were tested using an inhalation device (AEROLIZER®) with Apparatus 3 (Anderson Cascade Impactor), and the contents of the pharmaceutically active ingredients were measured from stages 1 to 5. The formulation of Example 1 was subjected to an additional test using a

different inhalation device (HANDIHALER®). The samples were analyzed using the analysis method used in Test Example 1 with four different flow rates, 10 L/min, 30 L/min, 60 L/min and 90 L/min. Also, relative humidity of the testing environment was kept in a range of 45 to 60% to minimize the effect of static electricity on the mixture particles during the inhalation. The results are shown in Figs. 1 to 3.

As shown in Figs. 1 to 3, the results of the contents during stages 1 to 5, which indicate the effective dose of the dry powder inhalation formulation of Examples 1 and 5 were relatively consistent at the range of 10 L/min to 90 L/min of the flow rate, and no fluctuation of particle size distribution in accordance with the flow rate changes was observed. On the contrary, the amount of the individual contents of Comparative Examples 2 and 3 was less than that of Examples 1 and 5, and a high fluctuation in the particle size distribution in accordance with the flow rate changes was observed as well. In the case of Comparative Example 2, the amount of lactose was too small, and the size of the carrier as well as the method for mixing were inappropriate so that a large amount of the active ingredients remained in the capsule after the inhalation of the formulation, and also the high fluctuation in the particle size distribution in accordance with the flow rate changes was observed. Also, in the case of Comparative Example 3, it seems that a considerable change in the particle size distribution was caused owing to inappropriate particle size of the compositions.

What is claimed is:

1. A dry powder for inhalation formulation comprising salmeterol xinafoate, fluticasone propionate, tiotropium bromide, and a carrier, having an average particle size in a range of 30 to 120 μm.

2. The dry powder for inhalation formulation of claim 1, whose average particle size is in a range of 55 to 65 μm.

3. The dry powder for inhalation formulation of claim 1, wherein the carrier is selected from the group consisting of monosaccharides, disaccharides, polysaccharides, polyalcohols and hydrates thereof.

4. The dry powder for inhalation formulation of claim 3, wherein the carrier is lactose monohydrate.

5. The dry powder for inhalation formulation of claim 1, wherein the dry powder for inhalation formulation is used for the prevention or treatment of respiratory diseases.

6. An inhalation formulation comprising the dry powder of claim 1.

7. The inhalation formulation of claim 6, wherein the amount of the carrier employed is in a range of 15 mg to 25 mg per unit dose of the formulation.

8. The inhalation formulation of claim 6, wherein salmeterol xinafoate, fluticasone propionate and tiotropium bromide are employed in amounts of 25 to 100 μg, 25 to 500 μg, and 5 to 50 μg, per unit dose of the formulation, respectively.

9. A method for preparing the dry powder for inhalation formulation of claim 1, which comprises the steps of:

(1) applying 5 to 20 wt% of the carrier, based on the total amount of the carrier, onto inner wall of a mixer;

(2) triturating salmeterol xinafoate, fluticasone propionate and tiotropium bromide with 5 to 20 wt% of the carrier, based on the total amount of the carrier; and

(3) mixing and pulverizing the triturated ingredients and the remaining carrier in the mixer prepared in Step (1) by applying a force not to substantially alter the size of the particles.

10. The method for preparing the dry powder for inhalation formulation of claim 9, wherein the average size particle of said pulverized ingredients is greater than 0.1 μm and less than or equal to 10 μm, and the average size particle of the pulverized carrier is in a range of 30 to 120 μm.

FIG. 1

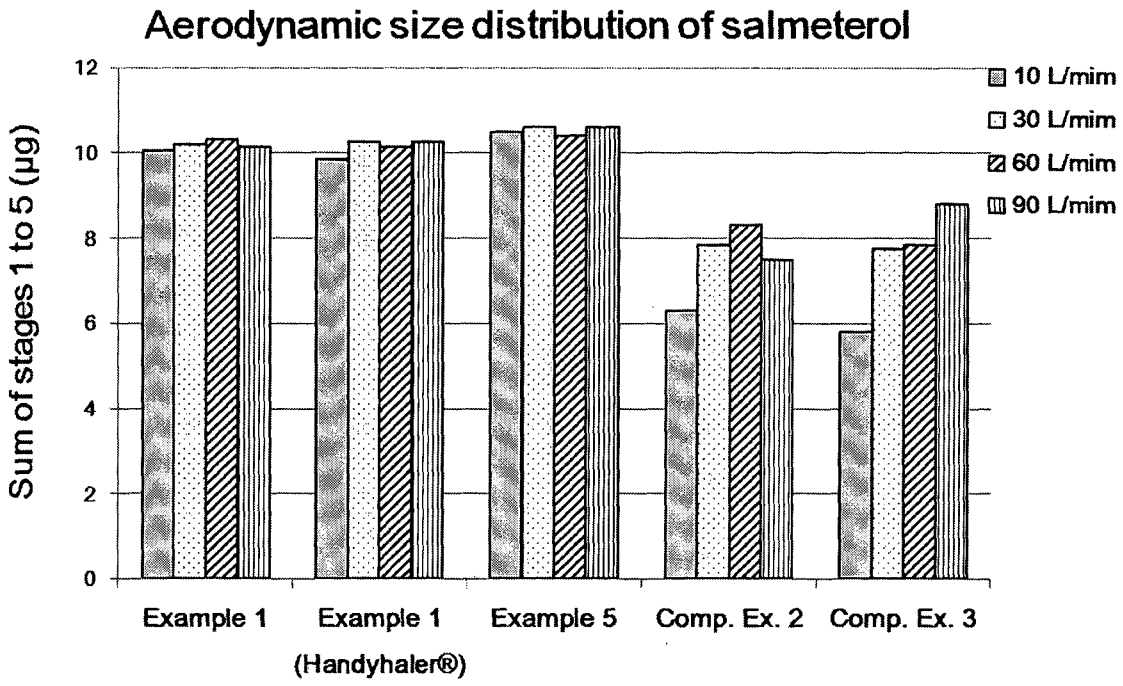

Aerodynamic size distribution of salmeterol
Sum of stages 1 to 5 (μg)
12
10
8
6
4
2
0
10 L/mim
30 L/mim
60 L/mim
90 L/mim
Example 1
Example 1 (Handyhaler®)
Example 5
Comp. Ex. 2
Comp. Ex. 3

FIG. 2

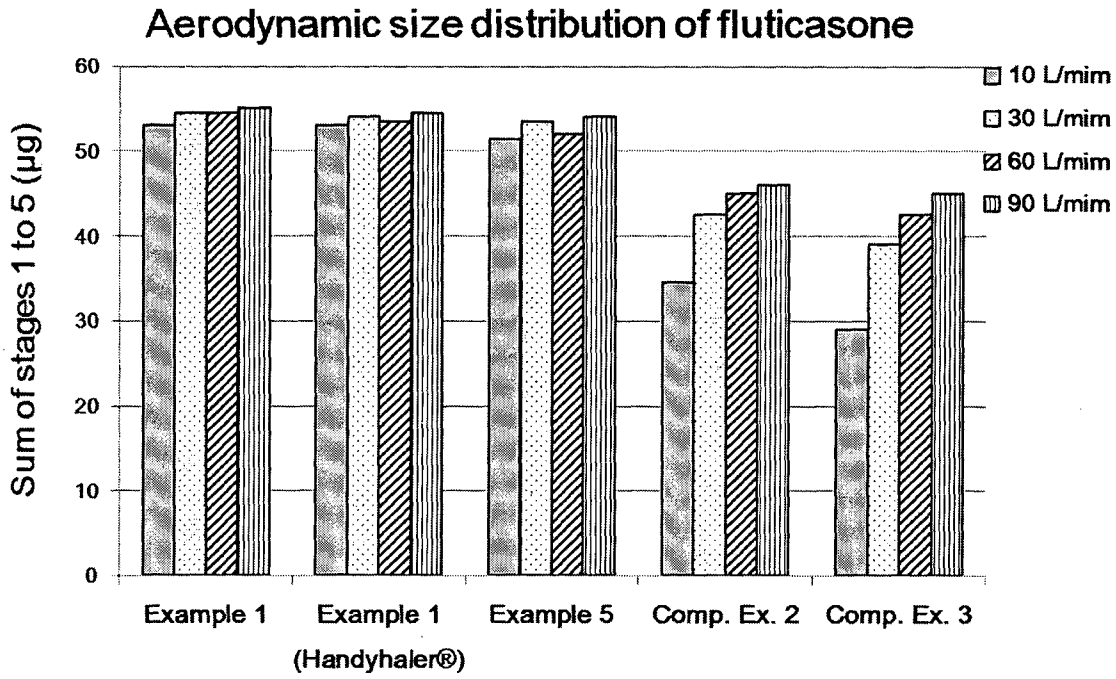
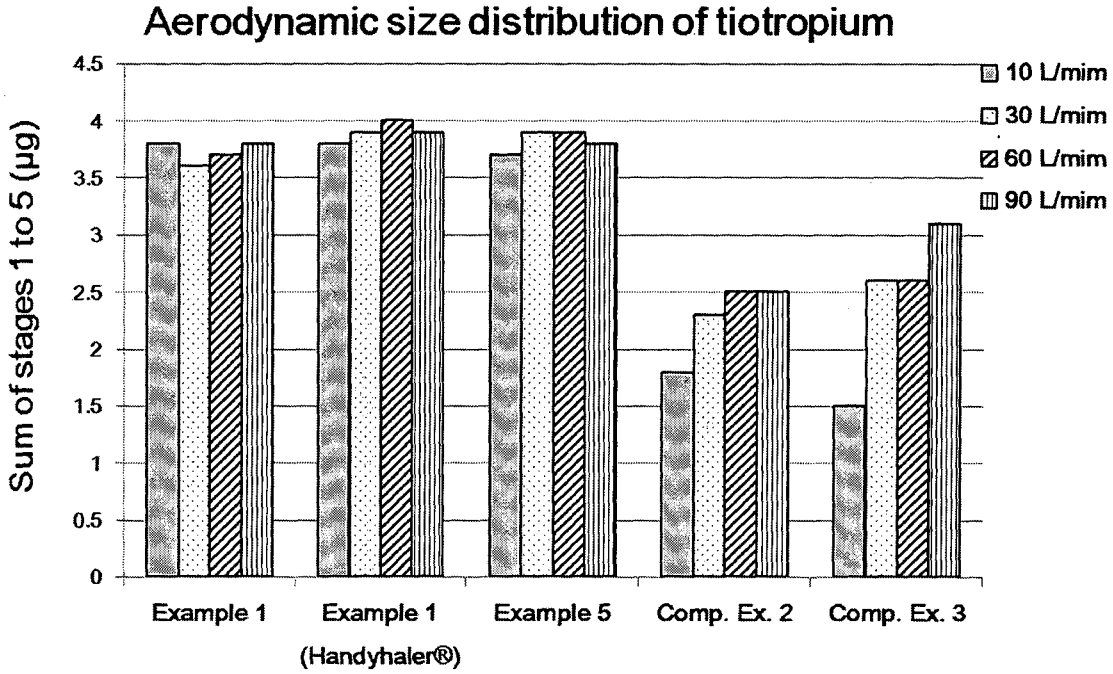

Aerodynamic size distribution of fluticasone
Sum of stages 1 to 5 (μg)
60
50
40
30
20
10
0
10 L/mim
30 L/mim
60 L/mim
90 L/mim
Example 1
Example 1 (Handyhaler®)
Example 5
Comp. Ex. 2
Comp. Ex. 3

FIG. 3


Aerodynamic size distribution of tiotropium
Sum of stages 1 to 5 (μg)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
10 L/mim
30 L/mim
60 L/mim
90 L/mim
Example 1
Example 1 (Handyhaler®)
Example 5
Comp. Ex. 2
Comp. Ex. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2013/004880

A. CLASSIFICATION OF SUBJECT MATTER

A61K 9/14(2006.01)i, A61K 9/16(2006.01)i, A61K 31/56(2006.01)i, A61K 31/166(2006.01)i

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 9/14; A61K 31/573; A61K 31/7016; A61K 9/12; A61K 31/166; A61K 9/16; A61K 31/56

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: salmeterol xinafoate, fluticasone propionate, tiotropium bromide, dry powder, inhalation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2010-0329996 A1 (LAINE, D. I.) 30 December 2010 See abstract; paragraphs [0003]-[0008], [0029]-[0034], [0045], and [0129]; and claims 1, 14, 23, 30, 31, and 38-40.	1-10
A	CAZZOLA, M. et al., `A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD`, Pulmonary Pharmacology & Therapeutics, 2007, Vol. 20, pages 556-561. See abstract; pages 557, 559, and 560; and figures 1-3.	1-10
A	KR 10-2009-0121338 A (CIPLA LTD.) 25 November 2009 See abstract; paragraphs [0025]-[0030]; claims 1, 2, 5, 11, 13, 22, 27, 28, 30, and 35; and examples 37-39.	1-10
A	SINGH, D. et al., `Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD`, Thorax, 2008, Vol. 63, pages 592-598. See abstract and page 593, right-column.	1-10

☒ 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
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"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
12 September 2013 (12.09.2013)	**13 September 2013 (13.09.2013)**

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2013/004880

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AARON, S. D. et al., `Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease`, Annals of Internal Medicine, 2007, Vol. 146, pages 545-555. See abstract.	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2013/004880

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2010-0329996 A1	30/12/2010	CN 101801378 A	11/08/2010
		EP 2197444 A1	23/06/2010
		JP 2010-539182 A	16/12/2010
		KR 10-2010-0063116 A	10/06/2010
		MX 2010002781 A	01/04/2010
		RU 2010108640 A	20/10/2011
		WO 2009-036243 A1	19/03/2009
KR 10-2009-0121338 A	25/11/2009	AU 2008-217586 A1	28/08/2008
		CA 2677573 A1	28/08/2008
		EP 2124915 A2	02/12/2009
		EP 2327403 A2	01/06/2011
		EP 2327403 A3	31/08/2011
		JP 2010-519195 A	03/06/2010
		US 2010-0063016 A1	11/03/2010
		US 2013-0074834 A1	28/03/2013
		WO 2008-102128 A2	28/08/2008
		WO 2008-102128 A3	08/01/2009

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代理人 郑斌 彭鲲鹏

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A61K 31/56(2006.01)
A61K 31/166(2006.01)

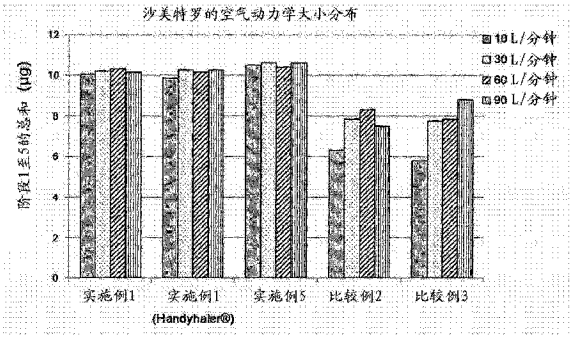
权利要求书1页 说明书13页 附图2页

(54)发明名称

用于吸入制剂的包含昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵的干粉及其制备方法

(57)摘要

提供了用于吸入制剂的包含作为药物活性成分的昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵以及载体的干粉，以及包含所述干粉的吸入制剂。本发明的具有良好含量均匀度并且表现为在流量变化时空气动力学大小分布变化小的干粉吸入制剂在施用后可有效地将所述药物活性成分递送至靶部位，因此可用于预防或治疗呼吸系统疾病，特别是哮喘和COPD。



CN 104363895 A

1. 用于吸入制剂的干粉，其包含昔萘酸沙美特罗、丙酸氟替卡松、噻托溴铵和载体，平均颗粒大小为 30μm 至 120μm。

2. 权利要求 1 所述的用于吸入制剂的干粉，其平均颗粒大小为 55μm 至 65μm。

3. 权利要求 1 所述的用于吸入制剂的干粉，其中所述载体选自单糖、二糖、多糖、多元醇及其水合物。

4. 权利要求 3 所述的用于吸入制剂的干粉，其中所述载体是乳糖一水合物。

5. 权利要求 1 所述的用于吸入制剂的干粉，其中所述用于吸入制剂的干粉用于预防或治疗呼吸系统疾病。

6. 吸入制剂，其包含权利要求 1 所述的干粉。

7. 权利要求 6 所述的吸入制剂，其中每单位剂量所述制剂中所述载体的使用量为 15mg 至 25mg。

8. 权利要求 6 所述的吸入制剂，其中每单位剂量所述制剂中昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵的使用量分别为 25μg 至 100μg、25μg 至 500μg 以及 5μg 至 50μg。

9. 用于制备权利要求 1 所述的用于吸入制剂的干粉的方法，其包括以下步骤：

(1) 将基于所述载体总量的 5wt％至 20wt％的所述载体施加于混合机的内壁上；

(2) 将昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵与基于所述载体总量的 5wt％至 20wt％的所述载体一起研磨；以及

(3) 在步骤 (1) 中准备的所述混合机中通过施加不显著改变所述颗粒之大小的力来混合和粉碎经研磨成分和其余载体。

10. 权利要求 9 所述的用于制备所述用于吸入制剂的干粉的方法，其中所述经粉碎成分的平均大小颗粒大于 0.1μm 且小于或等于 10μm，并且经粉碎载体的平均大小颗粒为 30μm 至 120μm。

用于吸入制剂的包含昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵的干粉及其制备方法

技术领域

[0001] 本发明涉及用于吸入制剂的包含昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵的干粉及其制备方法。

背景技术

[0002] 已经有多种药物以吸入制剂的形式用来治疗呼吸系统疾病(respiratory disease),例如哮喘和慢性阻塞性肺病(chronic obstructive pulmonary disease,COPD)。吸入制剂的一个特别的优点是仅需要少量药物活性成分就能达到期望的治疗效果;然而,这种制剂的缺点是仅一部分所施用药物活性成分将被递送至靶部位,或者存在很大的可能性将药物活性成分递送至不需要治疗的位置从而引起不良的副作用。因此,一直不断努力使所述制剂的疗效最大化,以实现向期望治疗效果的部位可靠地靶向递送并防止向不需要治疗的部位递送药物活性成分。

[0003] 为了有效施用吸入制剂,通过吸入含有药物的空气并将其递送到气道中来施用药物的吸入器已经广泛地用于治疗呼吸系统疾病。最常见的吸入器系统是定量吸入器(metered dose inhaler,MDI),自1956年获得批准后,其已经被广泛使用,并一度占据了80%的吸入器市场。然而,近年来,环境问题(例如臭氧层耗竭和全球变暖)的产生已经使研究兴趣转而集中于干粉吸入器(dry powder inhaler,DPI)。现阶段,研究人员着力于通过使用DPI制剂来弥补MDI制剂的缺点。MDI通常包含药物活性成分和作为抛射剂的压缩状态的溶剂,而压缩状态劣化了其稳定性;并且,由于喷射速度快,其过快地到达咽喉空间。然而,DPI却易于使用,并且仅包含粉末固体颗粒,因此在稳定性方面有优势(参见Martin J Telko和Anthony J Hickey,Dry Powder Inhaler Formulation,Respiratory Care,2005年9月,第50卷,No.9)。

[0004] 同时,测试了多种药物来预防和治疗呼吸系统疾病。例如,选择性β-2肾上腺素受体激动剂(β-2激动剂)可诱导支气管扩张,并且可用于缓解呼吸窘迫。β-2激动剂可大致分为短效β-2激动剂和长效β-2激动剂。短效β-2激动剂(例如沙丁胺醇、非诺特罗、左旋沙丁胺醇、特布他林等)提供立即的缓解,但是它们的反应时间非常短。相反,长效β-2激动剂(例如福莫特罗、茚达特罗、沙美特罗、妥洛特罗等)提供持久的支气管扩张,但是由于这些药物的正常反应时间短于12小时,所以需要患者每天施用两次或更多次。

[0005] β-2激动剂可缓解患者的支气管收缩,但是使用其他药物(例如类固醇)来治疗炎症,这是哮喘的另一个病因。类固醇的实例包括吸入皮质类固醇(inhaled corticosteroid,ICS),例如,倍氯美松、布地奈德、氟尼缩松、丙酸氟替卡松、糠酸莫美他松、曲安西龙等。

[0006] 此外,另一种被称为吸入抗胆碱能剂(anticholinergic)的药物类型是公知的稳定且有效的支气管扩张剂,其可用于治疗COPD。抗胆碱能剂可提高1秒用力呼气量(forced expiratory volume in 1second,FEV1)水平,防止静态或动态过度膨胀(肺过度膨胀)并

减小 COPD 的恶化。目前可得到的吸入抗胆碱能支气管扩张剂的数量有限，例如，迅速作用类型如异丙托溴铵、氧托溴铵等，以及长效类型如噻托溴铵等。

[0007] 全球哮喘防治创议 (Global Initiative for Asthma，GINA) 和全球慢性阻塞性肺疾病防治创议 (Chronic Obstructive Lung Disease，GOLD) 建议基于疾病症状进展的增量式治疗方法，其包括使用具有不同的或互补的作用机制的药物组合制剂。例如，给患有哮喘或 FEV1 水平低于 80％的 COPD 的患者开出长效 β-2 激动剂，而给伴随有 FEV1 水平低于 50％的呼吸窘迫的或经受频繁急性加重的 COPD 患者除了 β-2 激动剂外还开出 ICS。

[0008] 上述药物的若干组合是已知的，一个典型实例是包含昔萘酸沙美特罗和丙酸氟替卡松的吸入制剂（舒利迭 (Seretide)，GSK)。目前，舒利迭可用在 MDI(Evohaler) 和 DPI(Diskus) 中。舒利迭提供由长效 β-2 激动剂沙美特罗诱导的有效支气管扩张，以及由 ICS 丙酸氟替卡松引起的强抗炎作用。在以 DPI 制剂的形式提供的舒利迭准纳器制剂 (Seretide Diskus formulation) 的情况下，β-2 激动剂和吸入的皮质类固醇二者都可一次吸入，但是该制剂不表现持续的支气管扩张，因此患者需要每天施用两次或更多次。该制剂的另一个缺点在于，赋形剂的量太小而使得施用后无法在肺中感觉到，并且由于不能观察到施用制剂，有时不能恰当地递送剂量或者获取两次或更多次。

[0009] 此外，WO01/76601 中公开了包含迅速起始的抗胆碱能剂异丙托溴铵和长效 β-2 激动剂沙美特罗的组合治疗，并且美国专利 No.6,423,298 和 WO02/7672 公开了另一种使用抗胆碱能剂、β-2 激动剂以及类固醇的组合治疗。

[0010] 然而，所述制剂不涉及可同时发挥由 β-2 激动剂诱导的速效支气管扩张、由皮质类固醇诱导的抗炎作用以及由抗胆碱能剂诱导的持续的支气管扩张的三元组合制剂。

[0011] 最近，韩国专利公开出版物 No.10-2010-0063116 和 10-2009-0121338 提到了由 β-2 激动剂、皮质类固醇和抗胆碱能剂的三元组合制剂。然而，它们既没有考虑任何具体装置、有效剂量、其制造方法、包装类型、载体材料的颗粒大小等，也没有提供其评估数据。当使用不同类型的装置时，吸入制剂（尤其是干粉形式的吸入制剂）的压降值 (pressure drop value) 是不同的，并且递送至肺的活性成分的量也因包装形式（例如，泡罩包装对比胶囊包装）不同而不同。用作载体的赋形剂（例如，乳糖等）的性质和比例也可导致治疗效果的很大不同。此外，即使使用来自相同药物组的药物，也可能由于各药物的理化性质而导致诸如均匀度和存储稳定性的劣化等不期望的结果。

[0012] 虽然用于预防或治疗呼吸系统疾病的一些药物及其组合制剂是已知的，但是尚未开发出用于可同时一起施用长效 β-2 激动剂、吸入的皮质类固醇和抗胆碱能剂的三元组合制剂的具体组合物或其制备方法。因此，需要开发出这样的复合制剂的组合物，其可在单一的剂量中稳定且准确地施用所述三组药物从而改进患者的顺应性并提高患者携带所述制剂的便利性。

[0013] 发明概述

[0014] 因此，本发明的一个目的是提供用于包含昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵的吸入制剂的干粉，其具有良好的含量均匀度，并且表现为在流量变化时空气动力学大小分布 (aerodynamic size distribution) 变化小，在施用后可有效将所述药物活性成分递送至靶部位。

[0015] 本发明的另一个目的是提供包含所述干粉的吸入制剂。

[0016] 本发明的另一个目的是提供用于吸入制剂的干粉的制备方法。

[0017] 根据本发明的一个目的，提供了用于包含昔萘酸沙美特罗、丙酸氟替卡松、噻托溴铵以及载体的吸入制剂的干粉，其平均颗粒大小为 30μm 至 120μm。

[0018] 根据本发明的另一个目的，提供了吸入制剂，其包含所述用于吸入制剂的干粉。

[0019] 根据本发明的另一个目的，提供了用于吸入制剂的干粉的制备方法，其包括以下步骤：(1) 将基于载体总量为 5wt％至 20wt％的载体施加于混合机的内壁上；(2) 将昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵与基于载体总量的 5wt％至 20wt％的载体一起研磨；以及 (3) 将经研磨成分和其余载体放置于步骤 (1) 中准备的混合机中，然后用不足以显著改变颗粒大小的力粉碎混合物，然后混合。

[0020] 根据本发明的具有良好含量均匀度并且在流量变化时空气动力学大小分布变化小的用于吸入制剂的干粉可在施用后一起递送所述三种活性成分，从而增强患者携带所述制剂的便利性以及改进患者的顺应性，因此在治疗呼吸系统疾病（特别是哮喘和 COPD）时具有良好治疗顺应性。

[0021] 附图简述

[0022] 图 1 示出根据测试实施例 2 的沙美特罗的空气动力学大小分布分析。

[0023] 图 2 示出根据测试实施例 2 的氟替卡松的空气动力学大小分布分析。

[0024] 图 3 示出根据测试实施例 2 的噻托溴铵的空气动力学大小分布分析。

[0025] 发明详述

[0026] 根据本发明的用于吸入制剂的干粉包含平均颗粒大小为 30μm 至 120μm 的载体和作为活性成分的以下物质：作为长效 β-2 激动剂的昔萘酸沙美特罗、作为吸入皮质类固醇的丙酸氟替卡松和作为抗胆碱能剂的噻托溴铵。

[0027] 在本发明中，使用每种活性成分的特定盐或溶剂合物；但是，本领域技术人员可使用具有相同或类似活性的任何等价物来代替所述特定的盐或溶剂合物。所述等价物的实例包括但不限于其可药用盐、溶剂合物、水合物、对映体、衍生物、多晶型物和前药。

[0028] 为了将药物活性成分有效递送至肺以发挥药理学活性，各活性成分的颗粒必须微粉化。一般而言，适于通过吸入来施用的颗粒大小大于 0.1μm 并且小于或等于 10μm，优选大于 0.1μm 并且小于或等于 5μm。如果颗粒大小为 0.1μm 或更小，则颗粒可能从身体排出而不被支气管吸收。因此，根据 USP 34<601>“气溶胶、鼻喷雾剂、定量吸入器和干粉吸入器”（‘Aerosol，Nasal spray，Metered-dose inhaler and Dry powder inhaler’），提出了测量 MDI 制剂和 DPI 制剂的空气动力学大小分布的多种设备，例如装置 1 至 6。例如，当使用 USP 34<601> 的装置 3(Anderson Cascade Impactor) 时，可确定在阶段 1 至 5 期间收集的主要成分的空气动力学大小分布为 0.1μm 至 5μm，其使得能够通过测量所述量来预测吸入制剂在施用后可发挥药理学活性的有效量。一般而言，覆盖该范围的颗粒大小分布优选为用于吸入而测量的活性成分含量的 10％至 30％。

[0029] 然而，小颗粒由于其高的表面积 / 体积比值而热力学不稳定，并且过度的表面自由能可造成颗粒容易聚集。当颗粒聚集时，它们附着于胶囊或吸入装置的内壁，干扰粉末的释放。因此，可使用可药用赋形剂（即载体颗粒）以纠正该问题。

[0030] 具体地，优选使微粉化的药学活性成分附着于载体颗粒，以得到热力学稳定性，防止聚集，并因此在吸入后将颗粒有效地转运至身体内。此外，一旦施用，所述药物活性成分

在呼吸道中应该易于从载体颗粒的表面释放到达靶部位。一般而言，载体颗粒的颗粒大小相当大，以致于其不能直接到达靶部位，因此，如果活性成分不易从载体释放，则可到达靶部位的药物活性成分的量将显著降低。同时，载体颗粒的流动性随着颗粒颗粒大小的增大而增大，因此，载体的大小应当足够大以易于将颗粒转运出吸入装置。

[0031] 因此，用于吸入制剂的干粉所使用的载体的大小必须适于得到良好的流动性。在一个实施方案中，载体颗粒的大小为 30μm 至 120μm。这样的载体颗粒可与微粉化载体混合，以使药物活性成分颗粒均匀地附着于载体颗粒，并且使得在呼吸道中药物活性成分颗粒易于从载体颗粒释放。一般而言，这可通过将少量微粉化载体颗粒首先附着于载体颗粒的不规则表面来实现，使得微粉化载体颗粒附着于具有高表面能的表面以首先降低其表面能、降低总表面能并使载体颗粒具有均匀的表面能分布。微粉化载体颗粒的平均颗粒大小可以是 35μm 或更小，优选 30μm 或更小，更优选 25μm 或更小。此外，可以不影响吸入组合物的流动性的量来使用微粉化载体颗粒，例如基于载体颗粒总重的 0.1wt％至 20wt％。在一个实施方案中，可以 1wt％至 15wt％的量使用微粉化载体颗粒，在另一个实施方案中，可以 3wt％至 12wt％的量使用微粉化载体颗粒。一般而言，微粉化载体颗粒可与载体颗粒混合；或者，本发明中可使用具有均匀大小的市售载体颗粒。

[0032] 此外，载体颗粒的表面性质是影响药物活性成分从吸入装置释放或活性成分递送至靶部位的重要因素。需要药物活性成分具有与载体表面的足够的黏附力以允许良好的流动性，从而其可易于从吸入装置释放；同时，一旦其离开吸入装置，药物活性成分在呼吸道中必须易于从载体表面释放以到达靶部位，因此，难以维持载体表面与药物活性成分之间合适的黏附力。在本发明中，药物活性成分与载体经历软粉碎和混合方法，以在它们之间产生合适的黏附力。

[0033] 选择作为载体的赋形剂是吸入制剂（特别是包含两种或更多种药物活性成分的复合吸入制剂）组合物的重要因素。本发明可使用的赋形剂实例包括：单糖，例如葡萄糖、阿拉伯糖；二糖，例如乳糖、麦芽糖、蔗糖；多糖，例如淀粉、糊精或葡聚糖；多元醇，例如山梨醇、甘露醇和木糖醇；及其水合物。在本发明的一个实施方案中，使用单糖或二糖作为赋形剂；在本发明的另一个实施方案中，使用乳糖；在本发明的另一个实施方案中，使用乳糖一水合物。

[0034] 选择合适量的载体也是重要的。制剂中过量的载体不仅使患者由于过度的异物感而感到不舒服，而且还可由于作为异物的载体而引起哮喘。此外，如果使用的量太少，则难以得到载体和药物活性成分之间的均匀度，并且难以测量胶囊或泡罩包装中的一个剂量。因此，在本发明中，所使用的载体量为 15mg 至 25mg。所述量可不需要任何特殊设备来通过常规方法装载于胶囊或泡罩包装中，产生可在不作任何改变的常规制药设施中制造该制剂的优点。

[0035] 然而，在吸入制剂中，与载体量相比，药物活性成分的量非常小。因为常规的简单混合可导致难以实现含量均匀度，所以可使用其他方法如研磨来使活性成分与载体混合以解决该问题。研磨是指其中将药物活性成分和赋形剂以 1 ： 1 至 1 ： 4 的比例混合，例如 1 ： 1、1 ： 2 或 1 ： 4，然后反复地以相同的比例将赋形剂添加到所制备的混合物，直至用完所有赋形剂。然而，在吸入制剂包含的药物活性成分的颗粒大小非常小并且其占总含量相对非常小的部分的情况下，即使通过研磨法仍然存在含量均匀度的问题。

[0036] 因此，如韩国专利No.0849837所公开的，采用了使用筛选装置的分层混合法以维持含量均匀度。然而，在该方法中，在使用该方法前必须将大颗粒和小颗粒分开，并且10种或更多种（优选30种或更多种）级分中的每一种都需要穿过筛选装置，从而造成极大的不便。

[0037] 因此，本发明人努力克服了该问题，并发现，使药物活性成分和载体经历软粉碎和混合过程可解决本发明的吸入制剂的含量均匀度的问题。本文所用术语“软粉碎和混合”是指将粉末置于配备有球或切碎刀片的混合机中然后混合的过程，其中通过使混合机旋转来进行粉碎，并且通过球或切碎刀片以不足以显著改变颗粒大小（例如小于20％的颗粒大小变化的程度）的力来粉碎粉末颗粒。当长时间暴露于强的物理力时，载体颗粒的大小变小。如果载体颗粒的大小太小，则粉末的流动性劣化，并且粉末可能保留在吸入装置或胶囊中，从而导致难以将期望量的药物活性成分递送至靶部位。在一个优选实施方案中，本发明用于吸入制剂的干粉的平均颗粒大小范围为30μm至120μm。如果平均颗粒大小处于所述范围中，则药物活性成分的含量均匀度令人满意，并且颗粒大小分布不因流量变化而波动。但是，如果平均颗粒大小超过120μm，则含量均匀度劣化，并且在制剂被吸入时使药物活性成分保留在吸入装置或胶囊中。此外，如果平均颗粒大小小于30μm，则药物活性成分的有效量随流量而显著改变。在另一个优选实施方案中，用于本发明吸入制剂的干粉的平均颗粒大小为55μm至65μm。

[0038] 在所述混合过程中，将少量的载体施加于混合机的切碎刀片和壁上，接着将一定量的载体和药物活性成分研磨并筛分，然后进行软粉碎和混合。优选地，施加于切碎刀片和壁上的载体的量为基于载体总量的5wt％至20wt％；并且与药物活性成分一起研磨的载体的量为基于载体总量的5wt％至20wt％，但不限于此。药物活性成分具有非常小尺寸的颗粒和赋予其黏性的高表面能，因此如果先将它们放在混合机中，则由于它们可黏在混合机的切碎刀片和壁上而有很大的可能性损失活性成分。因此，可通过将合适量的具有良好流动性的载体施加于混合机的切碎刀片和壁上来防止这种情况发生。然后，将药物活性成分和载体进行研磨和筛分，接着进行软粉碎和混合过程。优选地，在40％至60％的相对湿度下进行该混合过程。如果相对湿度太低，则由于静电而难以进行混合过程；并且即使混合过程成功进行，仍然有很大可能性在该过程期间损失大量颗粒。此外，如果相对湿度太高，则颗粒倾向于吸收水分并形成聚集物。由于其吸湿性，所以在长期储存过程中如果暴露于过量湿气，则特别是昔萘酸沙美特罗的稳定性不能得到保证。

[0039] 如上文所解释的，本发明提供了用于吸入制剂的干粉的制备方法，其包括以下步骤：(1)将基于载体总量的5wt％至20wt％的载体施加于混合机的内壁上；(2)将昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵与基于载体总量为5wt％至20wt％的载体一起研磨；以及(3)将经研磨成分和其余载体放置于步骤(1)中准备的混合机中，然后用不足以显著改变颗粒大小的力研磨混合物，然后混合。

[0040] 同时，本发明提供了包含干粉的吸入制剂，其容纳在含有明胶或羟丙甲基纤维素的胶囊和药筒形式中或容纳在含有多层铝薄层的泡罩包装形式中，优选容纳于胶囊形式中。本发明制剂的胶囊尺寸优选为No.1至No.4。在本发明的一个实施方案中，所述胶囊尺寸为No.3。制备胶囊形式制剂的一个优点是其可以不需要任何特殊设备来制造。此外，装载本发明组合物的胶囊优选由透明材料制成。如果本发明制剂于透明胶囊中提供，则患

者在施用本发明制剂后，他们可凭借自己的肉眼检查他们是否已经适当摄取了所需要的药物。此外，患者在摄取制剂之前可用肉眼检查干粉的产品缺陷或品质劣化，例如聚集或变色。

[0041] 用于施用干粉的装置是指通过破坏、击打或使用任何其他方法打开胶囊以使经称重的组合物得以递送至患者的肺的装置。此外，所述装置还包含在空气进入所述装置处形成气流的进气口、当患者吸入空气时释放药物活性成分的出气口，以及过滤任何杂质的颗粒过滤器。这样的装置的实例当前可从市场获得，包括ROTAHALER® (GSK)、HANDIHALER® (Boehringer Ingelheim) 和AEROLIZER® (PLASTIAPE)。可用任何可使用胶囊组合物的装置（优选AEROLIZER®）来使用根据本发明的吸入制剂。在所述装置中，装置的中央有放置胶囊的孔，并且当按压侧面的按钮时，针状物 (pin) 出来穿刺出孔以使其准备好施用所述制剂。所述装置较小，并因此具有良好的便携性。

[0042] 在上文所述的 DPI 吸入装置中，使药物活性成分从胶囊中出来的驱动力是患者的吸力。在患者施用制剂时，所有 DPI 装置都具有由气流诱导的压降值，在空气动力学大小分布和含量均匀度测试中，根据气流变化的压降值可以是用于评价适于吸入制剂的有效量的重要变量。事实上，吸气流峰值将根据所使用的装置类型、患者年龄和疾病状况而不同，例如从 10L/ 分钟至 100L/ 分钟。美国药典建议，流量可控制为 0L/ 分钟至 100L/ 分钟，并且在整个吸入器中产生 4kPa 的压降的流量 (Q_{out}) 和由公式 T（秒）= 240/Q_{out} 获得的吸气时间 (T) 可用于评价测试结果。因此，优选地，本发明的制剂在流量变化时空气动力学大小分布变化小，从而在不同患者之间得到相似的药学效果。根据本发明的干粉吸入制剂具有这样的优点，三种药物活性成分的空气动力学大小分布不因流量变化而波动。

[0043] 因此，根据本发明的干粉吸入制剂可有效地使混合物从吸入装置释放；容易使药物活性成分在呼吸道中从载体释放，从而有效地将活性成分递送至靶部位；并且表现出经研磨的药物活性成分的良好含量均匀度并且在流量变化时空气动力学大小分布变化小。

[0044] 在根据本发明的干粉吸入制剂中，昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵可分别以 25μg 至 100μg、25μg 至 500μg 以及 5μg 至 50μg 每单位剂量的量使用。但是，可使用的量不限于此，并且可根据例如进行治疗的患者和疾病状况等多种因素来调节。

[0045] 本发明的包含沙美特罗、氟替卡松和噻托溴铵的干粉吸入制剂可有效控制呼吸道中的支气管缩小、炎症和黏液分泌，因此可用于治疗呼吸系统疾病，特别是哮喘和 COPD。

[0046] 在下文中，通过以下实施例来更具体地描述本发明，但是提供这些仅用于举例说明的目的，本发明并不限于此。

[0047] 实施例 1：干粉吸入制剂 I 的制备

[0048] 将 2mg 乳糖放置在混合机中，以施加于该混合机上。将根据表 1 中所列的组成的昔萘酸沙美特罗、丙酸氟替卡松和噻托溴铵与 2mg 乳糖一起研磨，并放置于该混合机中，然后，将剩下的乳糖放置于配备有球的混合机中，接着混合 20 分钟。将所得的混合物稳定化 12 小时或更久，并使用胶囊充填机装载于 No.3 尺寸的透明胶囊中。装载于胶囊中的含量偏差为 3.4%，是令人满意的，并且用 Sympatec HELOS 激光衍射传感器测得所述组合物的平均颗粒大小为 60.19μm。

[0049] [表 1]

[0050]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.2500
噻托溴铵	0.0225(噻托铵 0.018)
乳糖	20.0000
总计	20.3450

[0051]

[0052] 实施例 2:干粉吸入制剂 II 的制备

[0053] 重复实施例 I 的方法,不同之处在于,根据下表 2 使用 0.01125mg 量的噻托溴铵以获得干粉吸入制剂。装载于胶囊中的含量偏差为 3.1%,是令人满意的,并且所述组合物的平均颗粒大小为 58.34μm。

[0054] [表 2]

[0055]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.2500
噻托溴铵	0.01125(噻托铵 0.009)
乳糖	20.0000
总计	20.33375

[0056] 实施例 3:干粉吸入制剂 III 的制备

[0057] 重复实施例 I 的方法,不同之处在于,根据下表 3 使用 0.5000mg 量的丙酸氟替卡松以获得干粉吸入制剂。装载于胶囊中的含量偏差为 4.5%,是令人满意的,并且所述组合物的平均颗粒大小为 56.91μm。

[0058] [表 3]

[0059]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.5000
噻托溴铵	0.0225(噻托铵 0.018)

乳糖	20.0000
总计	20.5950

[0060]

[0061] 实施例 4 :干粉吸入制剂 IV 的制备

[0062] 重复实施例 I 的方法,不同之处在于,根据下表 4 使用 0.1000mg 量的丙酸氟替卡松和 0.01125mg 量的噻托溴铵以获得干粉吸入制剂。装载于胶囊中的含量偏差为 3.9%,是令人满意的,并且所述组合物的平均颗粒大小为 62.48μm。

[0063] [表 4]

[0064]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.1000
噻托溴铵	0.01125(噻托铵 0.009)
乳糖	20.0000
总计	20.18375

[0065] 实施例 5 :干粉吸入制剂 V 的制备

[0066] 重复实施例 I 的方法,不同之处在于,根据下表 5 使用 15mg 量的乳糖以获得干粉吸入制剂。装载于胶囊中的含量偏差为 4.8%,是令人满意的,并且所述组合物的平均颗粒大小为 63.57μm。

[0067] [表 5]

[0068]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.2500
噻托溴铵	0.0225(噻托铵 0.018)
乳糖	15.0000
总计	15.3450

[0069] 实施例 6 :干粉吸入制剂 VI 的制备

[0070] 重复实施例 I 的方法,不同之处在于,根据下表 6 使用 25mg 量的乳糖以获得干粉吸入制剂。装载于胶囊中的含量偏差为 3.2%,是令人满意的,并且所述组合物的平均颗粒

大小为 58.72μm。

[0071] [表 6]

[0072]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.2500
噻托溴铵	0.0225(噻托铵 0.018)
乳糖	25.0000
总计	25.3450

[0073] 比较例 1:干粉吸入制剂 VII 的制备

[0074] 根据表下表 7,将昔萘酸沙美特罗、丙酸氟替卡松、噻托溴铵和乳糖一起放置在混合机中,然后混合 60 分钟。将所得的混合物稳定化 12 小时或更久,并使用胶囊充填机装载于 No.3 尺寸的透明胶囊中。装载于胶囊中的含量偏差为 4.9%,是令人满意的,并且所述组合物的平均颗粒大小为 145.39μm。

[0075] [表 7]

[0076]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.2500
噻托溴铵	0.0225(噻托铵 0.018)
乳糖	20.0000
总计	20.3450

[0077] 比较例 2:干粉吸入制剂 VIII 的制备

[0078] 重复比较例 I 方法,不同之处在于,根据下表 8 使用 5mg 量的乳糖以获得干粉吸入制剂。所述组合物的平均颗粒大小为 140.56μm。

[0079] [表 8]

[0080]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.2500

噻托溴铵	0.0225(噻托铵 0.018)
乳糖	5.0000
总计	5.3450

[0081] 比较例 3:干粉吸入制剂 IX 的制备

[0082] 根据列于表 9 中的组成,使用乳糖(即平均颗粒大小为约 17μm 的 Respitose®ML006 (DMV))重复实施例 1 的方法,以制备混合物。将所得的混合物稳定化 12 小时或更久,并使用胶囊充填机装载于 No.3 尺寸的透明胶囊中。装载于胶囊中的含量偏差为 7.4%,不令人满意,并且通过激光衍射传感器 HELOS(Sympatec) 测得的所述组合物的平均颗粒大小为 14.63μm。

[0083] [表 9]

[0084]

成分	(mg)
昔萘酸沙美特罗	0.0725(沙美特罗 0.05)
丙酸氟替卡松	0.2500
噻托溴铵	0.0225(噻托铵 0.018)
乳糖	20.0000
总计	20.3450

[0085] 测试实施例 1:含量均匀度的评价

[0086] 对于在实施例 1 和 2 以及比较例 1 中得到的胶囊制剂,在以下条件下对沙美特罗、氟替卡松和噻托溴铵的含量均匀度进行评价。结果在表 10 至 12 中示出。根据韩国药典的剂量单元均匀度一节来计算根据各含量均匀度评价结果的接受值。

[0087]

$$\text{• 接受值} = |M - \bar{X}| + ks$$

[0088] M = 参比值,X = 各含量的平均值

[0089] k = 可接受性常数(当 n = 10 时为 2.4),s = 标准偏差

[0090] <沙美特罗和氟替卡松的分析条件>

[0091] 柱:填充有十八烷基甲硅烷基硅胶(直径 5μm)的不锈柱(内径为约 4.6mm,长度为 15cm)。

[0092] 流动相:含有 0.6% (w/v) 乙酸铵的甲醇:乙腈:水 = 50 : 16 : 34(v/v/v) 检测器:UV- 吸收检测器 (228nm 处的吸光度)

[0093] 柱温度:40℃

[0094] 流量 :1.0mL/ 分钟

[0095] 进样体积 :100μL

[0096] < 噻托铵的分析条件 >

[0097] 柱 :填充有十八烷基甲硅烷基硅胶 (直径 5μm) 的不锈柱 (内径为约 4.6mm, 长度为 15cm)。

[0098] 流动相 :通过将 300mL 乙腈添加至 700mL 在 1L 水中添加 1.79g 一水合庚烷磺酸钠而制备的溶液来制备的混合溶液, 并使用磷酸将 pH 值调节至 3.2。

[0099] 检测器 :UV- 吸收检测器 (240nm 处的吸光度)

[0100] 柱温度 :30℃

[0101] 流量 :2.0mL/ 分钟

[0102] 进样体积 :10μL

[0103] [表 10] 实施例 1 的干粉吸入制剂中活性成分的含量均匀度 (%)

[0104]

	沙美特罗 (%)	氟替卡松 (%)	噻托铵 (%)
1	96.2	102.6	96.2
2	94.6	96.7	96.8
3	94.9	103.7	99.3
4	103.2	94.6	101.0
5	96.8	92.6	99.0
6	104.6	98.5	101.7
7	99.0	103.1	99.0
8	106.2	96.6	97.4
9	102.6	103.6	99.9
10	102.5	103.9	100.9
平均值	100.1	99.6	99.1
S.D.	4.3	4.3	1.9
接受值	10.2	10.3	4.4

[0105] [表 11] 实施例 2 的干粉吸入制剂中活性成分的含量均匀度 (%)

[0106]

	沙美特罗 (%)	氟替卡松 (%)	噻托铵 (%)

1	96.4	100.2	99.4
2	98.7	100.5	99.1
3	98.6	100.7	101.3
4	96.4	99.6	101.5
5	100.8	96.9	96.1
6	98.6	100.6	100.6
7	100.8	100.0	98.4
8	100.8	100.7	101.5
9	100.9	100.6	101.4
10	96.5	98.5	92.9
平均值	98.9	99.8	99.2
S.D.	1.9	1.2	2.8
接受值	4.6	3.0	6.8

[0107]

[0108] [表 12] 比较例 1 的干粉吸入制剂中活性成分的含量均匀度（%）

[0109]

	沙美特罗（%）	氟替卡松（%）	噻托铵（%）
1	92.3	88.6	101.6
2	88.5	110.7	112.2
3	120.6	112.6	88.7
4	95.6	98.7	89.4
5	98.6	87.6	105.7
6	92.4	92.4	110.7
7	85.6	120.4	92.7
8	110.8	88.7	86.9

9	106.7	92.4	93.4
10	98.6	98.6	105.5
平均值	99.0	99.1	98.7
S.D.	10.8	11.6	9.5
接受值	26.0	27.8	22.9

[0110] 如以上的表 10 至 12 中所示，实施例 1 和 2 的干粉吸入制剂中三种活性成分的接受值小于 15，确保了所述制剂的均匀度。但是，比较例 1 的干粉吸入制剂中活性成分的接受值超过 20，因此示出含量均匀度的不一致性。

[0111] 测试实施例 2 :活性成分的空气动力学大小分布

[0112] 使用配备有装置 3(Anderson Cascade Impactor) 的吸入装置 (AEROLIZER®) 测试了实施例 1 和 5 以及比较例 2 和 3 中制备的干粉吸入制剂的空气动力学大小分布，并且在阶段 1 至 5 中测量药物活性成分的含量。使用不同的吸入装置 (HANDIHALER®) 对实施例 1 的制剂进行附加测试。使用测试实施例 1 中所用的分析方法，以 10L/ 分钟、30L/ 分钟、60L/ 分钟和 90L/ 分钟四种不同的流量分析了样品。此外，使测试环境的相对湿度保持在 45％至 60％的范围内，以在吸入期间使混合物颗粒上的静电作用最小化。结果在图 1 至 3 中示出。

[0113] 如图 1 至 3 所示，在阶段 1 至 5 期间，指示实施例 1 和 5 的干粉吸入制剂有效剂量含量的结果分别在 10L/ 分钟至 90L/ 分钟的流量范围内是恒定的，并且没有观察到因流量变化而导致的颗粒大小分布波动。相反，比较例 2 和 3 的含量的量小于实施例 1 和 5 的各含量的量，并且还观察到因流量变化导致的颗粒大小分布的高波动。在比较例 2 的情况下，乳糖的量太少，并且载体的大小和混合方法不适合，使得吸入制剂后大量活性成分残留在胶囊中，并且还观察到因流量变化导致的颗粒大小分布的高波动。此外，在比较例 3 的情况中，似乎由于不适当的组合物颗粒大小导致了颗粒大小分布的相当大的变化。

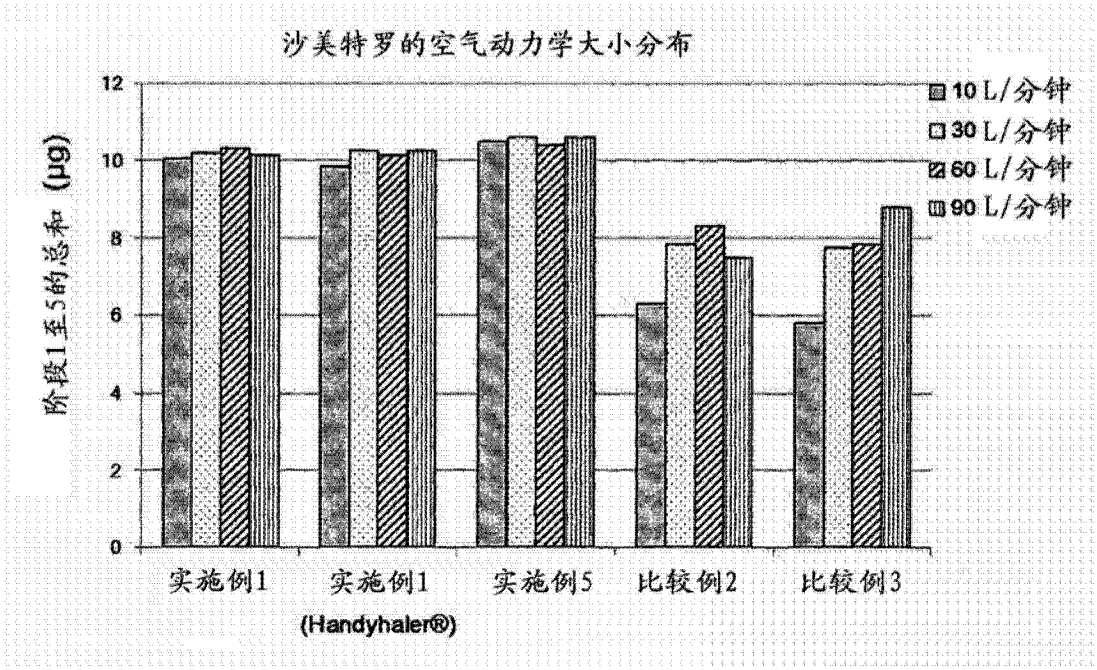

沙美特罗的空气动力学大小分布
阶段1至5的总和 (μg)
12
10
8
6
4
2
0
10 L/分钟
30 L/分钟
60 L/分钟
90 L/分钟
实施例1
实施例1
(Handyhaler®)
实施例5
比较例2
比较例3

图 1

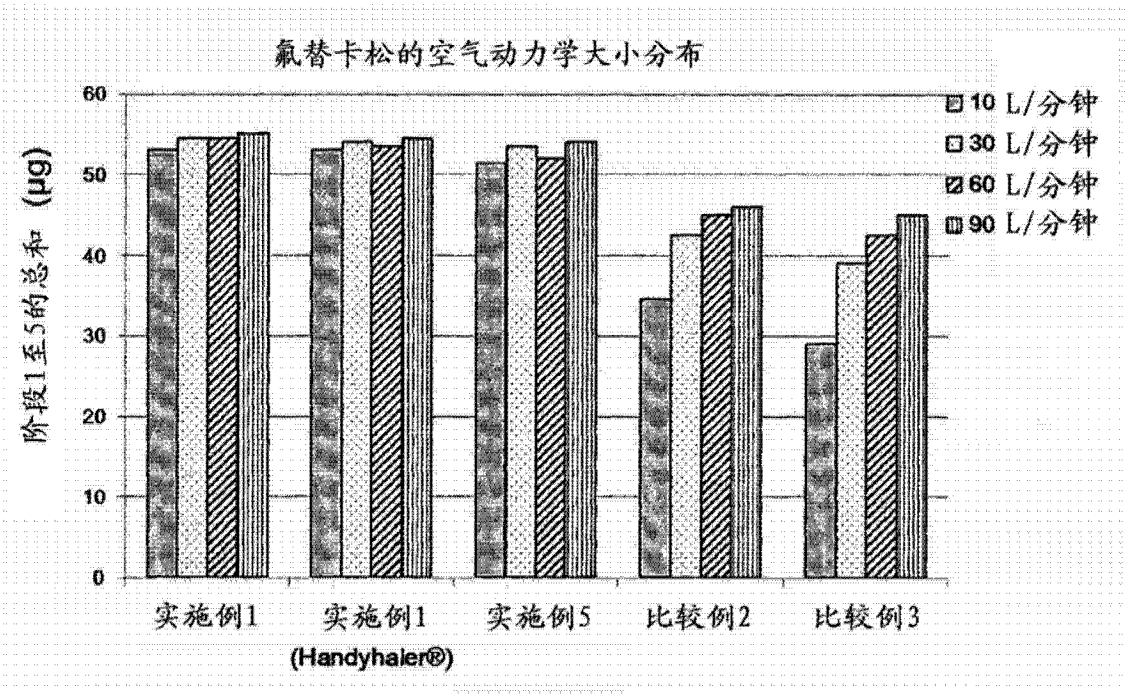

氟替卡松的空气动力学大小分布
阶段1至5的总和 (μg)
60
50
40
30
20
10
0
10 L/分钟
30 L/分钟
60 L/分钟
90 L/分钟
实施例1
实施例1
(Handyhaler®)
实施例5
比较例2
比较例3

图 2

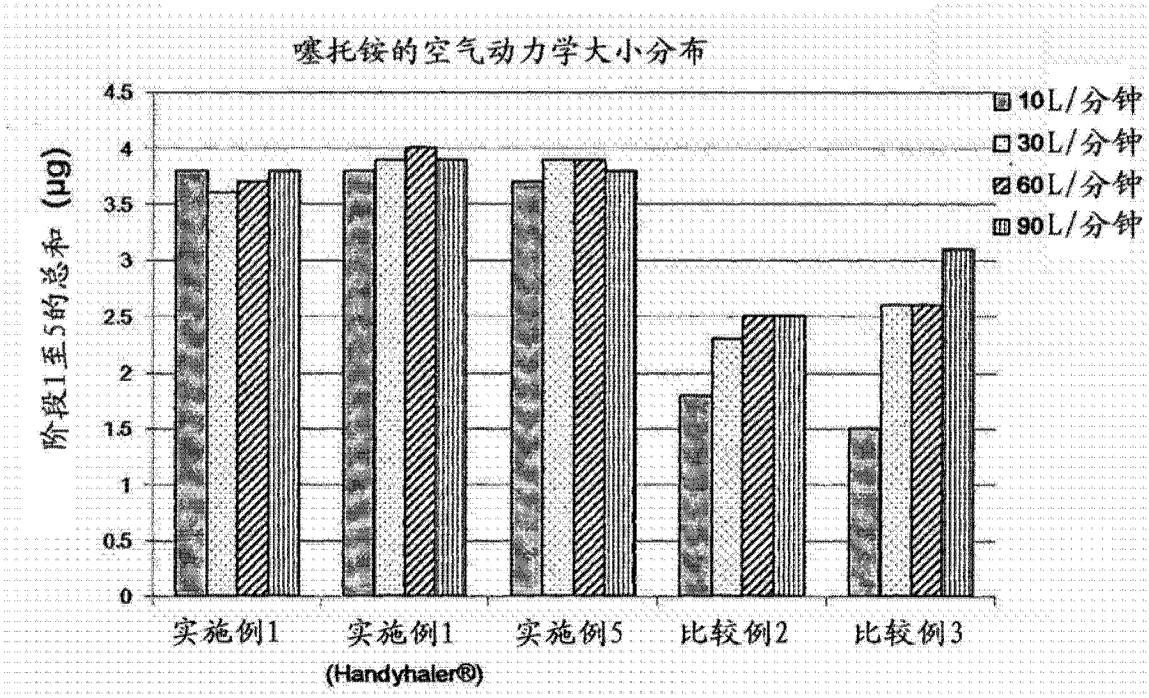

噻托铵的空气动力学大小分布
阶段1至5的总和 (μg)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
10L/分钟
30L/分钟
60L/分钟
90L/分钟
实施例1
实施例1
(Handyhaler®)
实施例5
比较例2
比较例3

图 3

Abstract

Provided is a dry powder for inhalation formulation comprising salmeterol xinafoate, fluticasone propionate and tiotropium bromide, as pharmaceutically active ingredients, and a carrier, and an inhalation formulation comprising same. The inventive dry powder inhalation formulation having good content uniformity and showing small changes in the aerodynamic size distribution in accordance with the flow rate changes can effectively deliver said pharmaceutically active ingredients to a target site upon administration, and thus can be useful in the prevention or treatment of respiratory diseases, particularly asthma and COPD.