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(54) Title: DRY POWDER FORMULATION WITH IMPROVED FLOW CHARACTERISTICS

(57) Abstract: The present invention relates to a new dry powder formulation developed in order to be used in respiratory tract diseases such as asthma and COPD.

DRY POWDER FORMULATION WITH IMPROVED FLOW CHARACTERISTICS

Purpose of the Invention

The present invention relates to a new dry powder formulation developed so as to be used in respiratory tract diseases such as asthma and COPD.

Background of the Invention

The dry powder formulation transmitted to the lungs of the patient by means of dry powder inhaler (DPI) is commonly used in treatment of respiratory tract diseases such as asthma and COPD. The dry powder formulation taken by the inhalation route affects very quickly since it reaches to the lungs directly and it provides a more effective and safe treatment even in small doses. However, in order to obtain these advantages, it is significantly important to adjust basic characteristics accurately such as particle size, intensity and flowability of the dry powder formulation. In addition, when the basic characteristics are adjusted, the production of a dry powder formulation is easily performed. The flowability characteristic is important particularly in the phases of the dry powder formulation such as blending, carrying and filling into the packages such as blister, capsule, reservoir, and it is important in advancement of the production without any problems. The fact that the dry powder formulation prepared has good flowability characteristic provides the dry powder formulation to be filled into the packages such as blister, capsule, reservoir easily; and consequently, it provides measurement accuracy.

The dry powder formulations taken by the inhalation route comprise the active agent and a large number of excipients compared to the active agent. The excipient particles provide to transmit the active agent particles having smaller particle size to to the lungs. In order to carry the active agent in sufficient amount to the lungs of the patient in each inhalation process, the active agent comprised in the formulation is required to be blended with the excipient homogeneously. Providing a homogeneous mixture is only possible when the formulation has a good flowability characteristic. The formulation having good flowability provides the active agent and the excipients comprised in the formulation to be mixed homogeneously as well as providing the formulation to be conveyed to the patient easily during inhalation and the amount of the active agent remained in the device to be minimized. The flowability of the formulation is considerably affected from the particle size distribution of the active agent and the excipients comprised in the formulation. The smaller the particle sizes are, the larger adhesion and cohesion forces among them become. Increase in adhesion and cohesion forces

causes the tendency of agglomeration of the particles to increase and therefore, the flowability of the formulation to worsen.

The dry powder formulations wherein the abovementioned problems are removed, which have good flowability and measurement accuracy are needed for treatment of respiratory tract diseases. According to this, the present invention relates to a dry powder formulation with good flowability used in treatment of respiratory tract diseases such as asthma and COPD.

Detailed Description of the Invention

The present invention relates to a dry powder formulation wherein the compressibility factor (Carr's Index) is in the range of 5% to 25%. The inventor has surprisingly found that in the case that the compressibility factor of the dry powder formulation is in the range of 5% to 25%, preferably in the range of 10% to 25%, more preferably in the range of 15% to 25%, the flowability improves; therefore, the abovementioned problems arising from flowability are removed. Furthermore, the inventor has found that the production of the formulation is performed with low cost and without any problems and the active agent amount remained in the device after each inhalation is minimized in the case that the compressibility factor is in the range of 5% to 25%, preferably in the range of 10% to 25%, more preferably in the range of 15% to 25%,.

The compressibility parameter is a value varying according to the ratio of bulk density to tapped density and it is calculated using the formula below:

$$C = 100 \times (1 - \frac{\rho_B}{\rho_T})$$

C: Compressibility parameter (Carr's index)

ϱ_B: Bulk density

ϱ_T: Tapped density

The tapped density is obtained by compacting the bulk density with vibrational motion. As seen from the formula, the compressibility parameter depends on only bulk density and tapped density. According to this, the inventor has provided the dry powder formulation to have a good flowability by adjusting the bulk density and tapped density in the manner that compressibility parameter of the formulation is in the range of 5% to 25%, preferably in the range of 10% to 25%, more preferably in the range of 15% to 25% during production.

In another aspect, the present invention relates to dry powder formulations wherein the ratio of bulk density:tapped density is in the range of 15:20 to 19:20.

The steps followed in production of the dry powder formulation of the present invention are as follows:

-the active agent and lactose having small particle size are micronized in the manner that the average particle size is minimum 3 μm; lactose having large particle size, on the other hand, is micronized separately in the manner that the average particle size is minimum10 μm.

-optionally, at least 10% of the excipient particles micronized by weight is subjected to spheronization process,

-the micronized active agents, the micronized excipients and, if available, the excipient particles subjected to spheronization process are blended,

-the dry powder formulation wherein the compressibility parameter is in the range of 5% to 25% is obtained,

-the formulation obtained is filled into capsules, blisters or reservoirs.

In another aspect, the present invention provides a dry powder formulation comprising an excipient having two different particle sizes. The dry powder formulation of the present invention comprises two excipient fractions having different average particle sizes as fine and coarse in addition to the active agent. The fact that the excipient particles are divided into two different fractions contributes to delivery of a sufficient amount of the active agent to the lungs of the patient in each inhalation process. The active agents and the fine excipients comprised in the formulation are carried by clinging to the active areas of the coarse excipients during inhalation. The number of the active areas varies according to particle size and particle morphology. During inhalation, the coarse excipient particles stick to the upper respiratory tracts of the patient. The active agents carried with the coarse excipient particles during inhalation easily split from the active areas of the coarse excipient thanks to the fine excipients clinging to the same active area and reach to the lungs of the patient with breath. If the smaller excipient particles are not available, the active agent also sticks to the upper respiratory tracts when the larger excipient particles stick there and it enters into the systemic circulation without being able to reach to the lungs. Therefore, the fact that the excipient comprised in the formulation of the present invention is divided into two different particle sizes provides advantage in treatment.

In another aspect, the present invention provides a dry powder formulation comprising coarse excipient particles along with fine excipient particles wherein the compressibility parameter is in the range of 5% to 25%, preferably in the range of 10% to 25%. In the formulation of the present invention, it has been seen that the fine excipient particles fill the voids between the coarse particles; thus, the tapped density and the bulk density of the dry powder formulation change. Hence, the change in the density causes the compressibility parameter of the dry powder formulation to change. By this way, the use of the excipient combination comprising the coarse excipient particles along with the fine excipient particles in the dry powder formulation of the present invention contributes to obtainment of the dry powder formulation wherein the compressibility parameter is in the range of 5% to 25%, preferably in the range of 10% to 25%.

The average particle size of the fine excipient particles comprised in the pharmaceutical composition of the present invention is in the range of 1 μm to 20 μm, preferably in the range of 2 μm to 12 μm, more preferably in the range of 3 μm to 10 μm. The average particle size of the coarse excipient particles is in the range of 10 to 1000 μm, preferably in the range of 100 to 600 μm and more preferably in the range of 150 to 300 μm. The percentage ratio of the excipient amount having larger average particle size comprised in the dry powder formulations of the present invention to total excipient amount by weight is at least as the compressibility parameter.

The present invention relates to dry powder formulations comprising an active agent and an excipient wherein

- the compressibility parameter of said formulation is in the range of 5% to 25%,
- formulation comprises two excipient fractions as fine and coarse having two different average particle sizes and
- the average particle size of the fine excipient is in the range of 2 μm to 12 μm and the average particle size of the coarse excipient is in the range of 10 to 1000 μm.

In the process used in preparation of the dry powder formulation according to the present invention, the excipients are preferably subjected to the spheronization process after they are micronized. According to this, minimum 10% of the excipient particles micronized by weight, for instance an amount in the range of 10%, 15%, 20%, 25%, 30%, 35% or 40% to 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100%, preferably an amount in the range of 25% to 95% by weight, more preferably an amount in the range of 50% to 90% is

optionally subjected to spheronization process. The excipient particles subjected to spheronization process is composed of only the fine excipient particles, only the coarse excipient particles or the combination of the fine and the coarse excipient particles. In the case that the excipient particles subjected to spheronization process are composed of the combination of the fine and the coarse excipient particles, the ratio of the fine excipient particles to the coarse excipient particles is in the range of 1:1 to 1:50 by weight, preferably in the range of 1:1 to 1:25 by weight, more preferably in the range of 1:1 to 1:10 by weight.

According to the present invention, the excipient comprised in the dry powder formulation can be selected from monosaccharides (glucose etc.), disaccharides (lactose, cellobiose, saccharose, maltose etc.), oligosaccharides and polysaccharides (dextrant etc.), polyalcohols (sorbitol, mannitol, xylitol etc.), salts (sodium chloride, calcium carbonate etc.), inositol and/or isomers thereof (myoinositol etc.) or a combination thereof, though it is preferably lactose.

According to the present invention, the excipient amount comprised in the dry powder formulation comprising active agent and the excipient is in the range of 0 to 50 mg and preferably in the range of 3 to 20 mg.

The present invention provides a dry powder formulation comprising the active agent in micronized sizes. The average particle size of the active agent comprised in the formulation of the present invention is in the range of 0.01 to 30 μm, preferably in the range of 0.05 to 10 μm and more preferably in the range of 1 to 5 μm.

The pharmaceutical composition of the present invention can be inhaled by means of single dose or multiple dose dry powder inhalation devices. According to this, the pharmaceutical composition of the present invention can be inhaled by means of these devices as carried in reservoir, capsule or blister. The active agent comprised in the dry powder formulation of the present invention is preferably a β_2 agonist. The active agent according to the present invention can be selected from carmoterol, formoterol, salmeterol and the combinations thereof and/or pharmaceutically acceptable derivatives thereof, though it is preferably formoterol.

Optionally, the dry powder formulation of the present invention can additionally comprise one or more substances selected from a group comprising mast cell stabilizer, anticholinergic, adrenergic agonist, glucocorticosteroid, xanthine, antileukotriene, PDEIV inhibitor, EGFR inhibitors, antiallergic, anti-inflammatory, antihistaminic and antimuscarinic agents.

In more detail, the dry powder formulation of the present invention can optionally comprise one or more substance selected from a group comprising mast cell stabilizers such as chromoglycate and nedocromile; anticholinergics such as ipratropium, tiotropium, glucopronium and oxitropium; β_2-agonists such as bambuterol, clenbuterol, salbutamol, fenoterol, terbutaline, carbuterol and pirbuterol; corticosteroids such as beclomethasone, ciclesonide, budesonide, fluticasone and mometasone; xanthines such as doxofylline, theobromine and theophylline; antileukotrienes such as montelukast, pranlukast, zafirlukast, ritolukast, sulukast, tomelukast, verlukast, iralukast, ablukast and cinalukast; antihistamines such as cetirizine, levocetirizine, loratadine, desloratadine, clemastine, clorphenamine, diphenhydramine and pheniramine; and PDE IV inhibitors such as roflumilast, piclamilast and cilomilast; preferably budesonide, ciclesonide, tiotropium and/or pharmaceutically acceptable derivatives thereof are used.

According to the present invention in another aspect, the active agent and/or pharmaceutically acceptable derivatives thereof comprised in the dry powder formulation comprises pharmaceutically acceptable solvates, hydrates, enantiomers or disastereomers, racemates, free base, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms of the active agent or a combination thereof.

According to the present invention, the amount of the active agent comprised in the dry powder formulation of the present invention is in the range of 1 μg to 750 μg, in other words in the range of 1 μg, 5 μg, 10 μg, 25 μg, 30 μg, 40 μg, 50 μg or 75 μg to 100 μg, 125 μg, 150 μg, 250 μg, 300 μg, 350 μg, 375 μg, 400 μg, 425 μg, 450 μg, 475 μg, 500 μg, 550 μg, 600μg, 650 μg, 700 μg or 750 μg, preferably in the range of 1 μg to 500 μg, in other words in the range of 1 μg, 5 μg, 15 μg, 25 μg, 50 μg or 75 μg or 100 μg to 125 μg, 150 μg, 175 μg, 250 μg, 300 μg, 350 μg, 400 μg, 450 μg, 475 μg or 500 μg and more preferably in the range of 1 μg to 400 μg.

The dry powder formulation of the present invention can be used in treatment of a number of respiratory tract diseases particularly in asthma, allergic rhinitis and chronic obstructive pulmonary disease (COPD). According to this, it is used in treatment of the respiratory tract diseases, but not limited to, asthma in any phases, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), exacerbation of airways hyperactivity, bronchiectasis, chronic obstructive pulmonary including emphysema and chronic bronchitis, airways or lung diseases (COPD, COAD or COLD), pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis. This treatment can be prophylactic or

symptomatic. Furthermore, the dry powder formulation of the present invention is particularly used in treatment of asthma and COPD.

Example

In order to prepare a dry powder formulation suitable to be inhaled by using the inhalation devices comprising blister, first of all formoterol and lactose having small particle size comprised in the formulation are micronized in the manner that the average particle size thereof is minimum 3 μm; lactose having large particle size, on the other hand, is micronized in the manner that the average particle size thereof is in the range of 80 μm to 90 μm. 85% of the lactose particles micronized are subjected to spheronization process. The micronized formoterol particles and the micronized lactose particles and the lactose particles subjected to the spheronization process are blended. The dry powder formulation wherein the compressibility parameter is 20% is obtained and the formulation obtained is filled into blisters.

Claims

1. A dry powder formulation comprising an active agent and an excipient, characterized in that,

- the compressibility parameter of said formulation is in the range of 5% to 25%,
- formulation comprises two excipient fractions as fine and coarse having two different average particle sizes and
- the average particle size of the fine excipient is in the range of 2 μm to 12 μm and the average particle size of the coarse excipient is in the range of 10 to 1000 μm.

2. The dry powder formulation according to claim 1, characterized in that the compressibility parameter of said formulation is in the range of 10% to 25%.

3. The dry powder formulation according to claims 1-2, characterized in that the average particle size of the fine excipient is in the range of 3 μm to 10 μm.

4. The dry powder formulation according to claims 1-3, characterized in that the average particle size of the coarse excipient is in the range of 100 to 600 μm.

5. The dry powder formulation according to claim 4, characterized in that the average particle size of the coarse excipient is in the range of 150 to 300 μm.

6. The dry powder formulation according to claims 1-5, characterized in that the percentage ratio of the amount of the coarse excipient in total excipient amount comprised in said dry powder formulation by weight is at least as the compressibility parameter.

7. The dry powder formulation according to claim 6, characterized in that the excipient or excipients are selected from monosaccharides (glucose etc.), disaccharides (lactose, cellobiose, saccharose, maltose etc.), oligosaccharides and polysaccharides (dextrant etc.), polyalcohols (sorbitol, mannitol, xylitol etc.), salts (sodium chloride, calcium carbonate etc.), inositol and/or isomers thereof (myoinositol etc.) or a combination thereof.

8. The dry powder formulation according to claim 7, characterized in that said excipient is lactose.

9. The dry powder formulation according to claims 1-8, characterized in that the average particle size of the active agent particles is in the range of 0.01 to 30 μm.

10. A method for preparation of the dry powder formulation according to claims 1-9, wherein said method comprises the following steps:

- micronizing the active agent and the excipient,
- blending the micronized active agent and the micronized excipient,

-obtaining a dry powder formulation wherein the compressibility parameter is in the range of 5% to 25%.

11. The method according to claim 10, characterized in that at least 10% of the micronized excipient by weight is subjected to spheronization process.

12. The method according to claims 10 and 11, wherein said method comprises the following steps:

-micronizing the active agent and the excipient,

-subjecting at least 10% of the micronized excipient by weight to spheronization process,

-blending the micronized active agent, the micronized excipient and the excipient subjected to spheronization process,

-obtaining the dry powder formulation wherein the compressibility parameter is in the range of 5% to 25%.

13. The method according to claims 10-12, characterized in that 25%-95% of the micronized excipient by weight is subjected to spheronization process.

14. The method according to claims 10 and 13, wherein said method comprises the following steps:

-micronizing the active agent and the excipient,

-a part of the micronized excipient in the range of 25% to 95% by weight is subjected to spheronization process,

-blending the micronized active agent, the micronized excipient and the excipient subjected to spheronization process,

-obtaining the dry powder formulation wherein the compressibility parameter is in the range of 5% to 25%.

15. The dry powder formulation according to claims 1-9, characterized in that the active agent is a β_2 agonist.

16. The dry powder formulation according to claim 15, characterized in that the active agent is selected from indacaterol, carmoterol, arformoterol, formoterol, salmeterol, salbutamol, bambuterol, salmeterol, carmoterol, clenbuterol, salbutamol, fenoterol, terbutaline, carbuterole, pirbuterol and the combinations thereof and/or pharmaceutically acceptable derivatives thereof.

17. The dry powder formulation according to claims 15-16, characterized in that said active agent is formoterol.

18. The dry powder formulation according to claims 15-16, characterized in that said active agent is carmoterol.

INTERNATIONAL SEARCH REPORT

International application No
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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14 A61K31/165 A61K9/00
ADD.

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

X See patent family annex.

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