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(54) Title: PREPARATION OF DRY POWDER FORMULATIONS COMPRISING TIOTROPIUM

(57) Abstract: The present invention relates to the process for the preparation of pharmaceutical formulations in dry powder form comprising tiotropium or pharmaceutically acceptable derivatives thereof in order to be used in symptomatic and/or prophylactic treatment of respiratory tract diseases, particularly asthma and COPD.

PREPARATION OF DRY POWDER FORMULATIONS COMPRISING TIOTROPIUM

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

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

Tiotropium is used in the treatment of respiratory tract diseases such as asthma and COPD. Tiotropium which has the chemical name of (1 α ,2 β ,4 β ,7 β)-7-[(hydroxidi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane belongs to the group of anticholinergics. Tiotropium was first disclosed in the patent numbered EP418716.

Proper flow characteristics of the dry powder formulations comprising tiotropium is of great importance for the inhalation of said formulation effectively and thus in terms of providing an effective treatment. When the dry powder formulation comprising tiotropium does not have good flow characteristics, it is observed that the formulation has low homogeneity and consequently dosing accuracy cannot be ensured during filling into blister cavities of a blister package.

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

Description of the Invention

The present invention relates to the process for the preparation of pharmaceutical formulations in dry powder form comprising tiotropium and/or pharmaceutically acceptable derivatives thereof.

The present invention relates to a process developed for production of a dry powder formulation comprising tiotropium. Said process comprises the following steps:

- I. The entire amount of excipient is divided into two fractions which are fine grained excipient and coarse grained excipient,
- II. The coarse grained excipient and the fine grained excipient are weighed in a container,
- III. The coarse grained and fine grained excipients are mixed in the container and the mixture of coarse grained- fine grained excipient mixture is obtained,
- IV. A hole is digged in the mixture of coarse grained- fine grained excipient mixture and tiotropium active agent is poured into this hole, then it is covered by the excipient which was set aside while digging the hole and tiotropium- excipient mixture is obtained,
- V. The tiotropium- excipient mixture is blended and the final dry powder mixture is obtained,
- VI. The final dry powder mixture is filled into the blister cavities of the blister package.

The inventors have surprisingly seen that the dry powder formulations comprising tiotropium prepared in accordance with the process of the present invention have good flow characteristics and have high homogeneity resulting in dosing accuracy and delivery of the sufficient amount of active agent to the lungs.

In step I of the process of the present invention, the excipient is divided into two fractions which are fine grained excipient and coarse grained excipient. Each fraction is micronized such that the average particle size of the fine grained excipient is in the range of 1 μm to 30 μm , preferably 2- 25 μm and more preferably 5- 20 μm . Total weight of the fine grained excipient is 3-55%, preferably 5%-50%, more preferably 10%-45% of the total weight of the formulation. Each fraction of the excipient divided into its fractions in the process of the present invention is micronized such that the average particle size of the coarse grained excipient is in the range of 20 μm to 120 μm , preferably 30- 100 μm and more preferably 45- 95 μm . Total weight of the coarse grained excipient is 40-95%, preferably 45%-90%, more preferably 50%-85% of the total weight of the formulation.

In another aspect, the present invention relates to the process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein the fine grained excipient having the average particle size in the range of 1 μm to 30 μm , preferably 2- 25 μm and more preferably 5- 20 μm is used.

In another aspect, the present invention relates to the process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein the fine grained excipient is used in an amount in the range of 3-55%, preferably 5%-50%, more preferably 10%-45% of the total weight of the formulation.

In another aspect, the present invention relates to the process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein the coarse grained excipient having the average particle size in the range of 20 μ m to 120 μ m, preferably 30- 100 μ m and more preferably 45- 95 μ m is used.

In another aspect, the present invention relates to the process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein the coarse grained excipient is used in an amount in the range of 40-95%, preferably 45%-90%, more preferably 50%-85% of the total weight of the excipient.

In Step II of the process of the present invention, the coarse grained excipient and the fine grained excipient are weighed in a container.

In step III of the process of the present invention, the coarse grained and fine grained excipients are mixed at 300- 3000 rpm, preferably 500- 2000 rpm for 30- 300 seconds, preferably 45- 180 seconds in the container and the mixture of coarse grained- fine grained excipient mixture is obtained.

In another aspect, the present invention relates to the process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein the coarse grained and fine grained excipients are mixed at 300- 3000 rpm, preferably 500- 2000 rpm for 30- 300 seconds, preferably 45- 180 seconds in the container and the mixture of coarse grained- fine grained excipient mixture is obtained.

In step IV of the process of the present invention, a hole is digged in the mixture of coarse grained- fine grained excipient mixture and tiotropium active agent is poured into the hole, then it is covered by the excipient which was set aside while digging the hole. A mixture of tiotropium and the excipient is obtained in this step.

In Step V of the process of the present invention, the tiotropium- excipient mixture obtained in Step IV is blended at 300- 3000 rpm, preferably 500- 2000 rpm for 1- 20 minutes, preferably 2- 10 minutes and the final dry powder mixture is obtained. The inventors have seen that blending

tiotropium- excipient mixture at 300- 3000 rpm, preferably 500- 2000 rpm for 1- 20 minutes, preferably 2-10 minutes results in providing a homogenous formulation comprising tiotropium and delivery of sufficient drug to the lungs effectively.

In another aspect, the present invention relates to the process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein the tiotropium- excipient mixture obtained in Step IV is blended at 300- 3000 rpm, preferably 500- 2000 rpm for 1- 20 minutes, preferably 2-10 minutes and the final dry powder mixture is obtained.

In Step VI of the process of the present invention, the final dry powder mixture is filled into the blister cavities of the blister package.

When the dry powder formulation prepared in accordance with the process of the present invention is inhaled from blister, the inventors have found that an effective inhalation is performed in the case that cavity volume of the blister comprising the drug in dry powder form comprising tiotropium and/or pharmaceutically acceptable derivatives thereof is in the range of 18-30 mm³, preferably in the range of 20 - 25 mm³, more preferably in the range of 21-24 mm³.

According to this, the present invention relates to the process characterized in that blister having cavity volume in the range of 18-30 mm³, preferably in the range of 20 to 25 mm³, more preferably in the range of 21-24 mm³ is used.

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

The present invention relates to the process characterized in that blister having fullness ratio in the range of 15-95%, preferably in the range of 20-85% and more preferably in the range of 50-80% is used.

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

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

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

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

The layer covering the inner surface of the cavity is a polymeric layer because of the fact that when the layer in contact with the dry powder formulation in the blister cavity is aluminium foil, some part of dry powder formulation adheres to the inner surface of the blister cavity due to porous structure of the aluminium foil and electrostatic forces and this causes uncontrolled dose inhalation. Polymers constituting the polymeric layer can preferably be selected from thermoplastic polymers such as polyethylene, polypropylene, polystyrene, polyolefin, polyamide, polyvinyl chloride, polyurethane or synthetic polymers.

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

In another aspect, the present invention relates to the process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein tiotropium

having average particle size in the range of 1 μm to 10 μm , preferably in the range of 1.5 μm to 7.5 μm , more preferably in the range of 1.5 μm to 5 μm is used as active agent.

In the dry powder formulation comprising tiotropium prepared in accordance with the process of the present invention, tiotropium active agent is used in an amount in the range of 2 to 60 μg , preferably in the range of 3 to 50 μg , more preferably in the range of 5 to 40 μg .

In the dry powder formulation comprising tiotropium prepared in accordance with the process of the present invention, the excipient is composed of fine grained excipient and coarse grained excipient. This excipient can be selected from monosaccharides (glucose etc.), disaccharides (lactose, saccharose, maltose or pharmaceutically acceptable hydrates, anhydrides or a combination thereof etc.), oligosaccharides and polysaccharides (dextran etc.), polyalcohols (sorbitol, mannitol, xylitol etc.), salts (sodium chloride, calcium carbonate etc.) or a combination thereof. Fine grained and coarse grained excipients are preferably lactose, more preferably lactose anhydride. According to the formulation prepared by the process of the present invention, the amount of the pharmaceutically acceptable excipient is in the range of 1-50 mg, preferably in the range of 2-40 mg, more preferably in the range of 5-35 mg.

The dry powder medicament prepared according to the process of the present invention is used in the treatment of many respiratory diseases, particularly in allergic or non-allergic asthma, allergic rhinitis and chronic obstructive pulmonary disease (COPD). Accordingly, the dry powder formulation prepared according to the process of the present invention is used in the treatment of, but not limited to, asthma at any stages, acute lung injury (ALI), acute respiratory distress syndrome (ARDS), exacerbation of airway hyperactivity, bronchiectasis, chronic obstructive pulmonary including emphysema and chronic bronchitis, respiratory diseases or lung diseases (COPD, COAD or COLD), pneumoconiosis, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis, byssinosis.

The examples below are given in order to provide better understanding of the present invention, yet they do not limit the scope of the invention.

EXAMPLE 1: Inhalation of dry powder formulations comprising tiotropium from capsule

Formulation content	% of amount by weight
Tiotropium	0.06%
Fine grained lactose	29.98 %
Coarse grained lactose	79.96%

The dry powder formulation comprising tiotropium can be obtained by the process of the present invention comprising the following steps;

- I. The entire amount of lactose is divided into two fractions which are fine grained lactose and coarse grained lactose,
- II. The coarse grained lactose and the fine grained lactose are weighed in a container,
- III. The coarse grained and fine grained lactose are mixed in the container and the mixture of coarse grained- fine grained lactose mixture is obtained,
- IV. A hole is digged in the mixture of coarse grained- fine grained lactose mixture and tiotropium active agent is poured into this hole, then it is covered by lactose powder which was set aside while digging the hole and tiotropium- lactose mixture is obtained,
- V. The tiotropium- lactose mixture is blended and the final dry powder mixture is obtained,
- VI. The final dry powder mixture is filled into the blister cavities of the blister package.

CLAIMS

1. A process for the preparation of the pharmaceutical formulation comprising tiotropium in the dry powder form wherein;
 - I. The entire amount of excipient is divided into two fractions which are fine grained excipient and coarse grained excipient,
 - II. The coarse grained excipient and the fine grained excipient are weighed in a container,
 - III. The coarse grained and fine grained excipients are mixed in the container and the mixture of coarse grained- fine grained excipient mixture is obtained,
 - IV. A hole is digged in the mixture of coarse grained- fine grained excipient mixture and tiotropium active agent is poured into this hole, then it is covered by the excipient which was set aside while digging the hole and tiotropium- excipient mixture is obtained,
 - V. The tiotropium- excipient mixture is blended and the final dry powder mixture is obtained,
 - VI. The final dry powder mixture is filled into the blister cavities of the blister package.
2. The process according to claim 1 wherein the coarse grained and fine grained excipients are mixed at 300- 3000 rpm for 30- 300 seconds in the container and the mixture of coarse grained- fine grained excipient mixture is obtained.
3. The process according to claims 1-2 wherein the coarse grained and fine grained excipients are mixed at 500- 2000 rpm for 45- 180 seconds in the container and the mixture of coarse grained- fine grained excipient mixture is obtained.
4. The process according to claims 1-3 wherein the tiotropium- excipient mixture obtained in Step IV is blended at 300- 3000 rpm for 1- 20 minutes and the final dry powder mixture is obtained.
5. The process according to claims 1-4 wherein the tiotropium- excipient mixture obtained in Step IV is blended at 500- 2000 rpm for 2-10 minutes and the final dry powder mixture is obtained.

6. The dry powder formulation comprising tiotropium prepared in accordance with the process according to claims 1-5 wherein the fine grained excipient has the average particle size in the range of 1 μm to 30 μm is used.
7. The formulation according to claim 6 wherein the fine grained excipient has the average particle size in the range of 2- 25 μm .
8. The formulation according to claims 6- 7 wherein the fine grained excipient has the average particle size in the range of 5- 20 μm .
9. The formulation according to claims 6- 8 wherein said formulation comprises the fine grained excipient in an amount in the range of 3-55% of the total weight of the formulation.
10. The formulation according to claims 6- 9 wherein the used coarse grained excipient has the average particle size in the range of 20 μm to 120 μm .
11. The formulation according to claim 10 wherein the used coarse grained excipient has the average particle size in the range of 30- 100 μm .
12. The formulation according to claims 10-11 wherein the used coarse grained excipient has the average particle size in the range of 45- 95 μm .
13. The formulation according to claims 6-12 wherein said formulation comprises the coarse grained excipient in an amount in the range of 40-95% of the total weight of the formulation.
14. The formulation according to claims 6-13 wherein said formulation comprises tiotropium having average particle size in the range of 1 μm to 10 μm .
15. The formulation according to claim 14 wherein said formulation comprises tiotropium having average particle size in the range of 1.5 μm to 7.5 μm .
16. The formulation according to claims 14-15 wherein said formulation comprises tiotropium having average particle size in the range of 1.5 μm to 5 μm .
17. The formulation according to claims 6-16 wherein said formulation comprises tiotropium in an amount in the range of 1-50 mg.
18. The formulation according to claim 17 wherein said formulation comprises tiotropium in an amount in the range of 2-40 mg.
19. The formulation according to claims 17-18 wherein said formulation comprises tiotropium in an amount in the range of 5-35.
20. The formulation according to claims 6-19 wherein said formulation comprises pharmaceutically acceptable excipient in the range of 1-50 mg.
21. The formulation according to claim 20 wherein said formulation comprises pharmaceutically acceptable excipient in the range of 2-40 mg.

22. The formulation according to claim 20 wherein said formulation comprises pharmaceutically acceptable excipient in the range of 5-35 mg.