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(54) Title: FORMULATION OF CALCIUM CHANNEL BLOCKER

(57) Abstract: The present invention relates to a dry powder formulation comprising at least one calcium channel blocker and tiotropium developed in order to be used in respiratory tract diseases such as asthma and COPD.

FORMULATION OF CALCIUM CHANNEL BLOCKER

Summary of the Invention:

The present invention relates to a dry powder formulation comprising at least one calcium channel blocker and tiotropium developed in order to be used in respiratory tract diseases such as asthma and COPD.

Background of the Invention:

Medicaments used in respiratory tract diseases such as asthma and COPD are generally β_2-agonists, glucocorticosteroids, leukotriene agonists, mast cell stabilizers and anticholinergics. Anticholinergics, which are the most commonly used medicaments today, are used particularly in asthma and COPD. Some of the examples of anticholinergics used in respiratory tract diseases are tiotropium, ipratropium, glycopyrrolate and atropine.

Recently, use of calcium channel blockers in respiratory tract diseases such as asthma and COPD have been started to be investigated. In the patent numbered WO2001092267, derivatives of dihydropyridine which is a calcium channel blocker was defined and use of these molecules in the treatment of asthma was disclosed. Although blockage of calcium channels seems like a good approach in the treatment of asthma and COPD, calcium channel blockers existing today cannot provide sufficient treatment when used alone. Furthermore, the formulations comprising calcium channel blockers in the prior art cannot be used by the inhalation route. It is also known that the formulations that can be used by the inhalation route cannot present sufficient efficiency.

In the present day, there is still need for a more efficient, simple treatment with reduced dose frequency in order to provide best control of respiratory tract diseases such as asthma and COPD. Therefore, new formulations that would be developed for use in the treatment of these diseases are still required.

Detailed Description of the Invention:

The inventor has surprisingly found that a more efficient treatment is provided with a formulation comprising at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof together with tiotropium in dry powder form that is an

anticholinergic agent in which the average particle size of the active agent is adjusted in the range of 1,5 to 4 μm. Furthermore, the inventor has found that the dry powder formulation comprising an active agent, average particle size of which is in the range of 1,5 to 4 μm, together with an excipient which have two different particle sizes as fine and coarse can be delivered to the lungs more effectively. Adjusting the particle sizes in the range of 1,5 to 4 μm, rate of the active agents which adsorb onto the excipient or excipients having two different average particle sizes is increased.

The present invention relates to a dry powder formulation comprising tiotropium that is an anticholinergic, at least one calcium channel blocker and/or its pharmaceutically acceptable derivatives and at least one pharmaceutically acceptable carrier in which the average particle size of the active agent is adjusted in the range of 1,5 to 4 μm and at least one carrier has two different average particle sizes.

In another aspect, the present invention provides a medicament used once a day with the dry powder formulation comprising tiotropium, at least one calcium channel blocker and/or its pharmaceutically acceptable derivatives and at least one pharmaceutically acceptable carrier. With this medicament, a treatment with reduced dose frequency can be applied. Thus, the present invention provides a treatment in which the progression of the patient can be traced more easily.

The present invention provides a dry powder formulation in which the average particle size of its active agent is adjusted in the range of 1,5 to 4 μm. According to the present invention, coarse particles were caught in the upper respiratory tract and could not go further after inhaled. An effective treatment has been provided with the active agents which have an average particle size in the range of 1,5 to 4 μm in the dry powder formulations of the present invention.

According to the present invention, at least one pharmaceutically acceptable calcium channel blocker and/or pharmaceutically acceptable derivatives thereof in the dry powder formulation can be selected from a group comprising amlodipine, azelnidipine, barnidipine, benidipine, clevidipine, felodipin, lercanidipine, nicardipine, nifedipine, nilvadipine, verapamil, gallopamil and diltiazem, and preferably it is nifedipine, nilvadipine, verapamil and diltiazem.

According to the present invention, at least one pharmaceutically acceptable calcium channel blocker and/or pharmaceutically acceptable derivatives thereof in the dry powder formulation

comprises solvates, hydrates, enantiomers or diastereomers, racemates, free base, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms of the calcium channel blocker and/or a combination thereof.

According to the present invention, the amount of at least one pharmaceutically acceptable calcium channel blocker and/or pharmaceutically acceptable derivatives thereof in the dry powder formulation is in the range of 0,01 mg to 100 mg and preferably in the range of 0,1 to 50 mg.

According to the present invention in another aspect, tiotropium and/or pharmaceutically acceptable derivatives thereof in the dry powder formulation comprises solvates, hydrates, enantiomers or diastereomers, racemates, free base, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms of tiotropium and/or a combination thereof; preferably, it is bromide salt. In addition, it could also be in hydrate, anhydrous and hemihydrates
forms.

According to the present invention, the amount of tiotropium and/or pharmaceutically acceptable derivatives thereof is in the range of 1 to 25 μg and preferably in the range of 5 to 20 μg.

According to the present invention in another aspect, the dry powder formulation comprises at least one carrier which has two different average particle sizes. In addition to the active agent, the dry powder formulation of the present invention can comprise excipient having two different average particle sizes as fine and coarse. Thus, the active agent can reach the lungs more easily during inhalation. Fine particles adsorb onto the active areas on the coarse particles that the formulation comprises. Fine particles also have active areas. Thus, the number of active areas required for the active agent to adsorb and be carried is increased. In another aspect, coarse particles may get caught in the upper respiratory tract. In this case, the fine particles on the active areas of the coarse particles are released with the active agents and effectively transmitted to the lungs. If a formulation lacks fine particles, when the coarse particles get caught in the upper respiratory tract, active agent is released there and cannot reach the lungs. In another aspect, fine particles can fly without coarse particles and remain in the patient's mouth. Consequently, it provides advantages in the treatment that cellobiose comprised in the dry powder formulation of the present invention has two different particle sizes.

Average radius of fine excipient particles comprised in the pharmaceutical composition of the present invention is smaller than 10 μm, preferably smaller than 5 μm and more preferably smaller than 3 μm. Average radius of coarse excipient particles, on the other hand, is in the range of 10 to 500 μm, preferably in the range of 50 to 300 μm and more preferably in the range of 100 to 200 μm.

The present invention provides a dry powder formulation in which the amount of fine excipient particles is 10% or less than 10% of total excipient weight.

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

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

In another aspect, the present invention provides administration of the medicament comprising tiotropium, at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof via dry powder inhalers.

In another aspect, the present invention provides administration of the medicament comprising tiotropium, at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof via single dose or multiple dose inhalers.

In another aspect, the present invention provides a method comprising administration of the medicament composition comprising tiotropium, at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof via dry powder inhaler in which the composition is stored in peelable blister packs, reservoir or capsules for treatment of people suffering respiratory diseases.

In the inhalers developed in order to administer medicament in dry powder form, a specific amount of medicament in dry powder form becomes ready for inhalation when the device is activated.

In the devices where the dry powder formulation is stored in reservoirs, the dry powder formulation comprising more than one dose resides in the reservoir of the device and one dose of the dry powder medicament is inhaled by the patient when the device is activated.

According to the present invention, the pharmaceutical composition comprising tiotropium, at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof can additionally comprise one or more active agents and/or pharmaceutically acceptable derivatives thereof selected from a group comprising mast cell stabilizer, anticholinergic, adrenergic agonist, glucocorticosteroid, xanthine, anti leukotriene, PDEIV inhibitor, EGFR inhibitor, anti-allergic, anti-inflammatory, antihistaminic and antimuscarinic substances.

According to the present invention, the pharmaceutical composition comprising tiotropium, at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof can additionally comprise one or more substances selected from a group comprising mast cell stabilizers such as chromoglycate and nedocromile; anticholinergics such as ipratropium, glycopyrronium and oxytropium; β_2-agonists such as carmoterol, formoterol, arformoterol, bambuterol, salmeterol, clenbuterol, salbutamol, fenoterol, terbutaline, carbuterol and pirbuterol; corticosteroids such as beclomethasone, ciclesonide, budesonide, fluticasone and mometasone; xanthines such as doxyphyllin, theobromine and theophylline; antileukotrienes such as montelukast, pranlucast, zafirlukast, ritolukast, sulukast, tomelukast, verlukast, iralukast, ablukast and cinalukast; antihistamines such as cetirizine, levocetirizine, loratadine, desloratadin, clemastine, chlorphenamine, diphenhydramine and pheniramine; PDEIV inhibitors such as roflumilast, piclamilast and cilomilast; preferably formoterol, ciclesonide, montelukast and/or pharmaceutically acceptable derivatives thereof.

The pharmaceutical composition comprising tiotropium, at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof according to the present invention can be used in the treatment of many respiratory diseases, particularly in asthma, allergic rhinitis and chronic obstructive pulmonary disease (COPD). Accordingly, these respiratory diseases can be, but not limited to, asthma at any stage, 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. This treatment can be prophylactic or

symptomatic. In addition, the composition of the present invention is especially used for symptomatic treatment of asthma and COPD.

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

EXAMPLE 1

A dry powder formulation suitable to be stored in blister packs for use in a multi-dose inhalation device comprises 9 parts of tiotropium, 400 parts of diltiazem having an average particle diameter in the range of 1,5 to 4 μm; and 9000 parts of lactose having an average particle diameter below 300μm and 1000 parts of lactose having an average particle diameter below 10 μm as carrier all of which were micronized in air jet mill.

The active agent tiotropium given in this example comprises all pharmaceutically acceptable racemates, enantiomers or diastereomers, solvates, esters, hydrates and/or the free base, polymorphs, amorphous and crystalline forms, and the active agent diltiazem comprises all pharmaceutically acceptable salts, solvates, esters, hydrates and/or enantiomers, polymorphs, amorphous and crystalline forms thereof. The pharmaceutically acceptable carrier given in this example can optionally be added in a higher or a lower amount.

EXAMPLE 2

A dry powder formulation which is suitable for a gelatine capsule used in capsule inhalator comprises 18 parts of tiotropium, 800 parts of nifedipine having an average particle diameter in the range of 1,5 to 4 μm; and 10000 parts of lactose having a particle diameter below 300μm and 900 parts of lactose having an average particle diameter below 10 μm as carrier all of which were micronized in air jet mill.

The active agent tiotropium given in this example comprises all pharmaceutically acceptable racemates, enantiomers or diastereomers, solvates, esters, hydrates and/or the free base, polymorphs, amorphous and crystalline forms, and the active agent nifedipine comprises all pharmaceutically acceptable salts, solvates, esters, hydrates and/or enantiomers, polymorphs, amorphous and crystalline forms thereof. The pharmaceutically acceptable carrier given in this example can optionally be added in a higher or a lower amount. The capsule in this example is made of gelatin; it can optionally be made of chitosan, starch and/or derivatives of starch, cellulose and/or cellulose derivatives or synthetic polymers.

Claims:

1. A dry powder formulation comprising tiotropium, at least one calcium channel blocker and/or pharmaceutically acceptable derivatives thereof and at least one pharmaceutically acceptable carrier in which the average particle size of the active agents is adjusted in the range of 1,5 to 4 μm; and at least one carrier has two different average particle sizes.
2. The dry powder formulation according to claim 1 characterized in that the calcium channel blocker and/or pharmaceutically acceptable derivatives thereof in said formulation is selected from a group comprising amlodipine, azelnidipine, barnidipine, benidipine, clevidipine, felodipin, lercanidipine, nicardipine, nifedipine, nilvadipine, verapamil, gallopamil and diltiazem.
3. The dry powder formulation according to claim 2 characterized in that the calcium channel blocker and/or pharmaceutically acceptable derivatives thereof in said formulation is selected from a group comprising nifedipine, nilvadipine, verapamil and diltiazem.
4. The dry powder formulation according to claim 1 characterized in that the amount of the calcium channel blocker and/or pharmaceutically acceptable derivatives thereof in said formulation is in the range of 0,01 to 100 mg.
5. The dry powder formulation according to claim 4 characterized in that the amount of the calcium channel blocker and/or pharmaceutically acceptable derivatives thereof in said formulation is in the range of 0,1 to 50 mg.
6. The dry powder formulation according to claim 1 characterized in that the amount of tiotropium and/or pharmaceutically acceptable derivatives thereof in said formulation is in the range of 1 to 25 mg.
7. The dry powder formulation according to claim 6 characterized in that the amount of tiotropium and/or pharmaceutically acceptable derivatives thereof in said formulation is in the range of 5 to 20 mg.
8. The dry powder formulation according to claim 1 characterized in that at least one pharmaceutically acceptable carrier comprised in said formulation has two different average particle sizes as coarse and fine.
9. The dry powder formulation according to claim 8 characterized in that the amount of the fine excipient particles is 10% or less than 10% of total excipient weight.
10. The dry powder formulation according to claim 7 characterized in that the average diameter of the fine excipient particles is less than 10 μm.

11. The dry powder formulation according to claim 10 characterized in that the average diameter of the fine excipient particles is less than 5 μm.
12. The dry powder formulation according to claim 11 characterized in that the average diameter of the fine excipient particles is less than 3 μm.
13. The dry powder formulation according to claim 8 characterized in that the average diameter of the coarse excipient particles is less than 500 μm.
14. The dry powder formulation according to claim 13 characterized in that the average diameter of the coarse excipient particles is less than 300 μm.
15. The dry powder formulation according to claim 14 characterized in that the average diameter of the coarse excipient particles is less than 200 μm.
16. The dry powder formulation according to claim 1 characterized in that at least one pharmaceutically acceptable excipient comprised in said formulation is selected from a group comprising monosaccharides (glucose, etc.), disaccharides (lactose, cellobiose, saccharose, maltose, etc.), oligosaccharides and polysaccharides (dextran, etc.), polyalcohols (sorbitol, mannitol, xyolitol, etc.), salts (sodium chloride, calcium carbonate, etc.), inositol and/or their isomers (myoinositol, etc.) or a combination thereof.
17. The dry powder formulation according to claim 16 characterized in that the pharmaceutically acceptable carrier is lactose.