(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 March 2012 (08.03.2012)

PCT

(10) International Publication Number
WO 2012/030308 A2

(51) International Patent Classification:
A61K 9/72 (2006.01)

(21) International Application Number:
PCT/TR2011/000198

(22) International Filing Date:
24 August 2011 (24.08.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2010/07250 1 September 2010 (01.09.2010) TR

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2012/030308 A2

(54) Title: FORMULATION COMPRISING CELLOBIOSE

(57) Abstract: The present invention relates to a pharmaceutical composition comprising a carrier and one or more than one active agents developed in order to be used in the treatment of respiratory tract diseases such as asthma and COPD.

FORMULATION COMPRISING CELLOBIOSE

Purpose of the Invention:

The present invention relates to a pharmaceutical composition comprising a carrier and one or more than one active agents developed in order to be used in the treatment of respiratory tract diseases such as asthma and COPD.

Background of the Invention:

Administration of the drugs by the inhalation route has an important place in the treatment of respiratory tract diseases such as asthma and COPD since the drugs given by the inhalation route directly reach the lungs and start their activity there. Active agents are used in pretty little amounts as they directly reach the target area. To this respect, both for production of the formulation and its administration in effective doses, one or more excipients are required in addition to the active agent. Formulation is diluted and carried with the excipients. According to this, formulations comprise excipients more than active agents.

To enable effective inhalation of dry powder formulations, there have been many studies conducted in the prior art in order to select the excipient and adjust the features of the excipient selected such as particle size, percentage by weight. The patent numbered EP0464171 disclosed that the particle size of the carrier comprised in the dry powder formulation could be in the range of 5 to 1000 μm. While it is possible to adjust the particle size of the carrier so as to ensure a more effective inhalation, one can also add another excipient along with the carrier. The patent numbered WO8705213 relates to a dry powder formulation comprising a lubricant in addition to the carrier. Both of these patents in the prior art particularly emphasize lactose. Furthermore, it is also seen that lactose is used in the products on the market such as FORADİL® and ASTMEROL®. However, although lactose is a good carrier, it leads to many problems due to its hygroscopic nature. With hygroscopic lactose, the dry powder formulation may be agglomerated and adhere to the surfaces. Since this adhesion also comprises the active agents, amount of the active agent in the formulation that reaches the patient's mouth decreases, therefore the quality of the treatment. Today, there is still need for novel formulations that would be developed in order to improve the quality of the treatment and minimize the specified problems. Moreover, there is still need for a simple, more effective treatment with reduced dose frequency.

Detailed Explanation of the Invention:

The inventor has surprisingly found that therapeutic effect is increased when long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof are carried with cellobiose. In the case that cellobiose is used as carrier in the dry powder formulations of the present invention, it has been seen that the rate of agglomeration of the formulation and adhesion to the device surfaces is decreased. By this means, the amount of active agent reaching the mouth therefore the lungs of the patient increases. Thus, it provides a more effective treatment with reduced dose frequency.

The present invention provides a pharmaceutical composition comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof as active agent and cellobiose as carrier developed in order to be used in the treatment of respiratory diseases such as asthma and COPD.

In another aspect, the present invention provides a dry powder formulation comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof and cellobiose.

According to the present invention, the amount of cellobiose in the dry powder formulation comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof is in the range of 0-50 mg and preferably in the range of 3-20 mg.

In another aspect, the present invention provides a medicament in which the average particle size of cellobiose that the pharmaceutical composition comprises is in the range of 0,01 to 1000 μm, preferably in the range of 5 to 500 μm. In the present invention, amount of active agent reaching the mouth and lungs of the patient is increased by adjusting the particle size of the carrier.

In another aspect, the present invention provides a pharmaceutical composition comprising cellobiose which has two different particle sizes. The dry powder formulation of the present invention can comprise cellobiose which has two different particle sizes as coarse and fine in addition to the active agent. 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 particle size of cellobiose 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 particle size of the coarse cellobiose particles, on the other hand, 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.

According to the present invention, long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof in the medicament formulation comprises pharmaceutically acceptable solvates, hydrates, enantiomers or diastereomers, racemates, free base, organic salts, inorganic salts, esters, polymorphs, crystalline forms and amorphous forms of long-acting β_2-agonist or a combination thereof.

According to the present invention, long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof comprised in the dry powder formulation can be selected from a group comprising salmeterol, bambuterol, clenbuterol, formoterol, arformoterol, carmoterol, indacaterol, milveterol, olodaterol or a combination thereof, though it is probably formoterol, arformoterol and carmoterol.

According to the present invention, amount of the active agent in the dry powder formulation comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof is in the range of 0,01 to 25 μm, preferably in the range of 0,1 to 20 μm and more preferably 0,5 to 15 μm.

According to another aspect, the present invention provides a medicament comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof in micronized sizes. Average particle size of long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof 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. Adjustment of particle sizes is very important for medicaments administered by the inhalation

route. Coarse particles can be caught in the upper respiratory tract after inhaled and this makes it harder for the particles to reach the lungs.

The present invention provides inhalation of the medicament comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof as active agent and cellobiose as carrier via dry powder inhalers.

In another aspect, the present invention provides inhalation of the dry powder formulation comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof and cellobiose from a capsule or blister.

In another aspect, the present invention provides administration of the dry powder formulation comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof and cellobiose in aerosol form. The term "aerosol" refers to dispersion or suspension of a liquid, solution or solid particles in air or gas. According to this, the dry powder formulation can be administered in aerosol form which is characterized by containing propellant gas or not.

According to the present invention, the dry powder formulation comprising cellobiose can additionally comprise other excipients. These excipients 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 isomers (myoinositol, etc.) or a combination thereof.

According to the present invention, the pharmaceutical composition comprising long-acting β_2-agonist 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 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 long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof can additionally comprise one or more substances and/or pharmaceutically acceptable derivatives thereof selected from a group comprising anticholinergics such as tiotropium, ipratropium, glycopyrronium and oxytropium; β_2-agonists such as salbutamol, fenoterol, terbutaline, carbuterol and pirbuterol; corticosteroids such as beclomethasone, budesonide, ciclesonide, fluticasone and mometasone; xanthines such

as doxyphyllin, theobromine, theophylline and aminophylline; antileukotrienes such as montelukast, pranlucast, zafirlukast, ritolukast, sulukast, tomelukast, verlukast, iralukast, ablukast and cinalukast; PDEIV inhibitors such as roflumilast, piclamilast and cilomilast; antihistamines such as levocetirizine, desloratadin, fexofenadine, vapitadine and alcaftadine.

The pharmaceutical composition comprising long-acting β_2-agonist 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.

Claims:

1. A pharmaceutical composition comprising long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof as active agent and cellobiose as carrier.
2. The pharmaceutical composition according to claim 1 characterized in that the amount of cellobiose comprised in said composition is in the range of 0-50 mg.
3. The pharmaceutical composition according to claim 2 characterized in that the amount of cellobiose comprised in said composition is in the range of 3-20 mg.
4. The pharmaceutical composition according to claim 1 characterized in that the average particle size of cellobiose comprised in said composition is in the range 0,01 to 1000 μm.
5. The pharmaceutical composition according to claim 1 characterized in that cellobiose comprised in said composition has two different average particle sizes.
6. The pharmaceutical composition according to claim 5 characterized in that the average particle size of fine cellobiose particles is smaller 10 μm.
7. The pharmaceutical composition according to claim 6 characterized in that the average particle size of fine cellobiose particles is smaller 5 μm.
8. The pharmaceutical composition according to claim 7 characterized in that the average particle size of fine cellobiose particles is smaller 3 μm.
9. The pharmaceutical composition according to claim 5 characterized in that the average particle size of coarse cellobiose particles is in the range of 10 to 1000 μm.
10. The pharmaceutical composition according to claim 9 characterized in that the average particle size of coarse cellobiose particles is in the range of 100 to 600 μm.
11. The pharmaceutical composition according to claim 10 characterized in that the average particle size of coarse cellobiose particles is in the range of 150 to 300 μm.
12. The pharmaceutical composition according to claim 1 characterized in that long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof is selected from a group comprising salmeterol, bambuterol, clenbuterol, formoterol, arformoterol, carmoterol, indacaterol, milveterol, olodaterol or a combination thereof.
13. The pharmaceutical composition according to claim 12 characterized in that long-acting β_2-agonist and/or pharmaceutically acceptable derivatives thereof is selected from a group comprising formoterol, carmoterol or a combination thereof.
14. The pharmaceutical composition according to claim 1 characterized in that said compositions additionally comprises one or more agents and/or pharmaceutically acceptable derivatives thereof selected from a group comprising anticholinergic,

adrenergic agonist, glucocorticosteroid, xanthine, anti leukotriene, PDEIV inhibitor, EGFR inhibitor, anti-allergic, anti-inflammatory, antihistaminic and antimuscarinic substances.