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CA 2803418 A1 2011/12/29

(21) 2 803 418

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2011/05/30
(87) Date publication PCT/PCT Publication Date: 2011/12/29
(85) Entrée phase nationale/National Entry: 2012/12/20
(86) N° demande PCT/PCT Application No.: EP 2011/058804
(87) N° publication PCT/PCT Publication No.: 2011/160920
(30) Priorité/Priority: 2010/06/22 (EP10166903.4)

(51) Cl.Int./Int.Cl. *A61K 9/14* (2006.01), *A61K 31/439* (2006.01), *A61K 9/00* (2006.01), *A61P 11/06* (2006.01), *A61P 11/08* (2006.01)

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(54) Titre : FORMULATION DE POUDRE SECHE COMPRENANT UN MEDICAMENT ANTIMUSCARINIQUE
(54) Title: DRY POWDER FORMULATION COMPRISING AN ANTIMUSCARINIC DRUG

(57) Abrégé/Abstract:
The invention relates to a dry powder formulation suitable for the inhalatory administration by means of a dry powder inhaler, comprising an antimuscarinic drug as active ingredient. The invention also relates to the process for the preparation of the formulation and to its use in the prevention and/or treatment of a wide range of conditions including respiratory disorders.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2011 (29.12.2011)

PCT

(10) International Publication Number
WO 2011/160920 A1

(51) International Patent Classification:
A61K 9/14 (2006.01) *A61P 11/06* (2006.01)
A61K 31/439 (2006.01) *A61P 11/08* (2006.01)
A61K 9/00 (2006.01)

(21) International Application Number:
PCT/EP2011/058804

(22) International Filing Date:
30 May 2011 (30.05.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10166903.4 22 June 2010 (22.06.2010) EP

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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, 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:

— *with international search report (Art. 21(3))*

WO 2011/160920 A1

(54) Title: DRY POWDER FORMULATION COMPRISING AN ANTIMUSCARINIC DRUG

(57) Abstract: The invention relates to a dry powder formulation suitable for the inhalatory administration by means of a dry powder inhaler, comprising an antimuscarinic drug as active ingredient. The invention also relates to the process for the preparation of the formulation and to its use in the prevention and/or treatment of a wide range of conditions including respiratory disorders.

DRY POWDER FORMULATION COMPRISING AN ANTIMUSCARINIC DRUG

FIELD OF THE INVENTION

The invention relates to a dry powder formulation suitable for the inhalatory administration by means of a dry powder inhaler, comprising an antimuscarinic drug as active ingredient.

The invention also relates to the process for the preparation of the formulation and to its use in the prevention and/or treatment of a wide range of conditions including respiratory disorders.

BACKGROUND TO THE INVENTION

Airway obstruction characterizes a number of severe respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD). Events leading to airway obstruction include oedema of airway walls, increased mucous production and inflammation.

Drugs for treating respiratory diseases such as asthma and COPD are currently administered through inhalation. One of the advantages of the inhalatory route over the systemic one is the possibility of delivering the drug directly at site of action, avoiding any systemic side-effects, thus providing a more rapid clinical response and a higher therapeutic ratio.

An important class of therapeutic agents used as bronchodilators is represented by the muscarinic receptor antagonist inhibitors belonging to the class of the quaternary ammonium salts, and in particular by the selective M3 receptor antagonists (hereinafter M3 antagonists).

For examples, M3 antagonists have been disclosed in WO 02/051841, WO 03/053966 and WO2008/012290.

Additional M3 receptor antagonists having high potency and long duration of action, that, once adsorbed, are degraded to inactive compounds

which are deprived of any systemic side effects typical of muscarinic antagonists, are object of a co-pending application n. PCT/EP2009/008870, incorporated herein by reference.

In particular, these latter compounds turned out to be particularly selective and endowed with a high potency.

Therefore, said compounds may provide significant therapeutic benefit in the treatment of respiratory diseases such as asthma and COPD, when administered by inhalation.

Said drugs could be administered to the respiratory tract by inhalation in the form of dry powder by means of suitable inhalers known as dry powder inhalers (DPIs).

The aim of the present invention is to provide an inhalable dry powder composition that comprises the above compounds as active ingredients.

Optimally said formulation shall exhibit good flowability, good uniformity of distribution of the active ingredient and adequate chemical and physical stability in the device before use.

It shall also give rise to a good respirable fraction as well as deliver an accurate therapeutically active dose of the active ingredient.

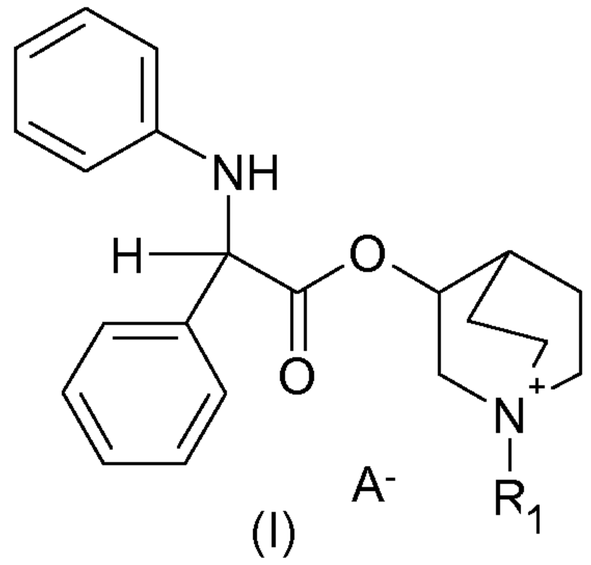
SUMMARY OF THE INVENTION

The invention relates to a dry powder formulation suitable for the inhalatory administration by means of a dry powder inhaler, comprising an aminoester derivative of formula (I), acting as muscarinic receptor antagonist.

The invention also relates to the process for the preparation of the formulation, to its use in the prevention and/or treatment of a wide range of conditions including respiratory disorders, such as chronic obstructive pulmonary disease (COPD) and asthma, to packages comprising an inhalable dry powder formulation and a dry powder inhaler.

DETAILED DESCRIPTION OF THE INVENTION

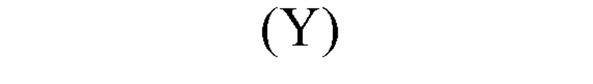
The compositions of the invention are pharmaceutical formulations in the form of inhalable dry powder, comprising, as active ingredient, micronized particles of a compound of general formula (**I**)



(I)

wherein:

$\mathbf{R_1}$ is a group of formula **(Y)**



(Y)

wherein

p is 0 or an integer from 1 to 4;

P is absent or is selected from the group consisting of O, S, SO, SO_2 and CO;

W is selected from the group consisting of H, aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, SH, NO_2, CN, COOH and NH_2;

A^- represents a physiologically acceptable anion;

and particles of a physiologically acceptable pharmacologically-inert solid carrier.

In the present description, unless otherwise stated, the term “halogen” includes fluorine, chlorine, bromine and iodine atoms.

The expression “aryl” refers to mono-, bi- or tri-cyclic ring systems which have 6 to 20 ring atoms, preferably from 6 to 15 and wherein at least one ring is aromatic.

The expression “heteroaryl” refers to mono- or bi-cyclic ring systems with 5 to 20 ring atoms, preferably from 5 to 15, in which at least one ring is aromatic and in which at least one ring atom is a heteroatom or heteroaromatic group (e.g. N, NH, S or O).

Examples of suitable aryl or heteroaryl monocyclic systems include, for instance, thiophene, benzene, pyrrole, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridine, imidazolidine, furan radicals and the like.

Examples of suitable aryl or heteroaryl bicyclic systems include naphthalene, biphenylene, purine, pteridine, benzotriazole, quinoline, isoquinoline, indole, isoindole radicals and the like.

Advantageously, the physiologically acceptable anion A^- is selected from the group consisting of chloride, bromide, iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulfonate.

In a first preferred embodiment, **p** is 1, **P** is absent and **W** is H.

In a second preferred embodiment, **p** is 1, **P** is CO and **W** is phenyl or thiophenyl.

In a third preferred embodiment, **p** is 2, **P** is O and **W** is phenyl.

In a fourth preferred embodiment, **p** is 3, **P** is O and **W** is phenyl.

The terms “active drug”, “active ingredient”, “active” and “active substance”, “active compound” and “therapeutic agent” are used as synonymous.

The terms “muscarinic receptor antagonists”, “antimuscarinic drugs” and “anticholinergic drugs” are used as synonymous.

The term “substantially pure” means a compound having an optical

purity higher than 90% based on the weight of said compound, advantageously higher tan 95% w/w preferably higher than 98% w/w, more preferably higher than 99% w/w.

By "single therapeutically effective dose" it is meant the quantity of active ingredient administered at one time by inhalation upon actuation of the inhaler.

Said dose may be delivered in one or more actuations, preferably one actuation (shot) of the inhaler.

"Actuation" refers to the release of active ingredient from the device by a single activation (e.g. mechanical or breath).

One aspect of the invention provides a pharmaceutical formulation, in the form of inhalable dry powder, comprising one or more compounds of formula (I) as active ingredients, and particles of a physiologically acceptable pharmacologically-inert solid carrier.

The invention provides a dry powder inhaler comprising the inhalable dry powder of the invention.

The invention also relates to the use of the inhalable dry powder formulation of the invention as a medicament.

A further aspect of the invention refers to the use of the inhalable dry powder of the invention for the prevention and/or treatment of an inflammatory or obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD).

A still further aspect of the present invention refers to a method of preventing and/or treating an inflammatory or obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD), which comprises administration by inhalation of an effective amount of the inhalable dry powder of the invention.

Finally the present invention is directed to a package comprising an

inhalable dry powder formulation of the invention and a dry powder inhaler.

In general terms, the particle size of particles is quantified by measuring a characteristic equivalent sphere diameter, known as volume diameter, by laser diffraction.

The particle size can also be quantified by measuring the mass diameter by means of suitable known instruments such as, for instance the sieve analyser.

The volume diameter (VD) is related to the mass diameter (MD) by the density of the particles (assuming a size independent density for the particles).

In the following description, the particle size is expressed in terms of mass diameter (MD) and the particle size distribution is expressed in terms of: i) the mass median diameter (MMD) which corresponds to the diameter of 50 percent by weight or volume respectively, of the particles, and ii) the MD in micron of 10% and 90% of the particles, respectively.

The terms MMD and mean particle size are used as synonymous.

The term “good flowability” refers to a formulation that is easily handled during the manufacturing process and is able to ensure an accurate and reproducible delivering of the therapeutically effective dose.

Flow characteristics can be evaluated by measuring the Carr’s index; a Carr’s index of less than 25 is usually taken to indicate good flow characteristics.

The expression “good homogeneity” refers to a formulation wherein, upon mixing, the content uniformity of the active ingredient, expressed as relative standard deviation (RSD), is less than 5%.

The expression “chemically stable” refers to a formulation that meets the requirements of the ICH Guideline Q1A referring to “Stability Testing of new Active Substances (and Medicinal Products)”.

The expression “physically stable in the device before use” refers to a

formulation wherein the active particles do not substantially segregate and/or detach from the surface of the carrier particles during fabrication of the dry powder and in the delivery device before use.

The tendency to segregate can be evaluated according to Staniforth et al. J. Pharm. Pharmacol. 34,700-706, 1982 and it is considered acceptable if the distribution of the active ingredient in the powder formulation after the test, expressed as relative standard deviation (RSD), does not change significantly with respect to that of the formulation before the test.

The expression "respirable fraction" refers to an index of the percentage of active particles which would reach the deep lungs in a patient.

The respirable fraction, also termed fine particle fraction, is evaluated using a suitable *in vitro* apparata such as Multistage Cascade Impactor or Multi Stage Liquid Impinger (MLSI) according to procedures reported in common Pharmacopoeias.

It is calculated by the ratio between the delivered dose and the fine particle mass (formerly fine particle dose).

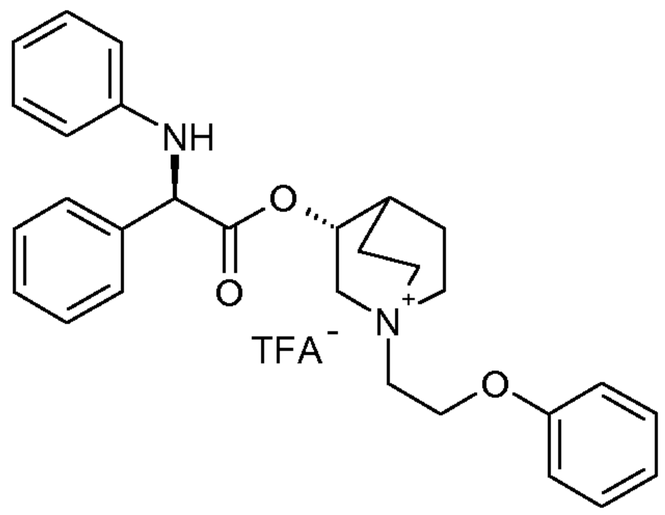
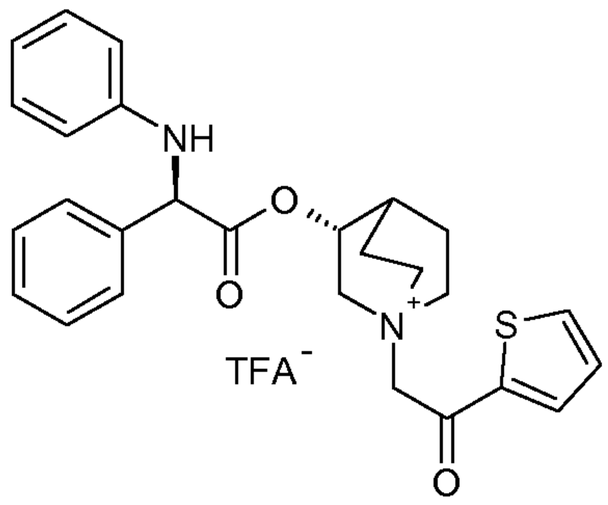
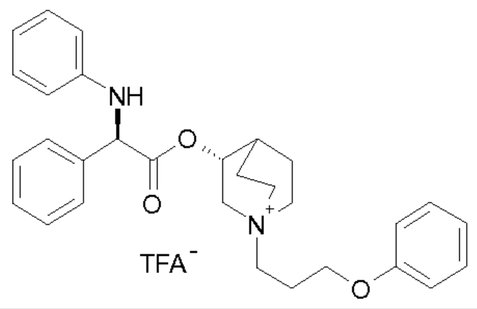
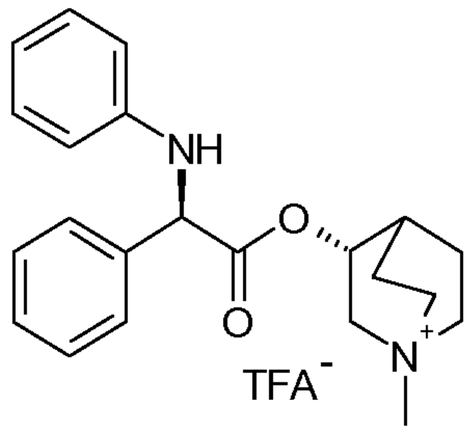
The delivered dose is calculated from the cumulative deposition in the apparatus, while the fine particle mass is calculated from the deposition on Stages 3 (S3) to filter (AF) corresponding to particles $\leq$ 4.7 microns.

A respirable fraction higher than 30% is an index of good inhalatory performances.

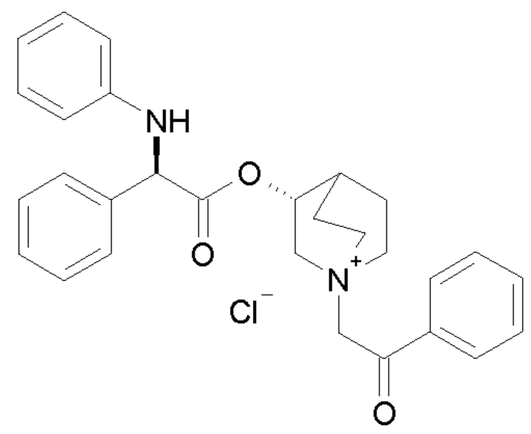
The expression "accurate therapeutically active dose of the active ingredient" refers to a formulation wherein the variation between the mean delivered daily dose and the mean emitted dose is equal to or less than 15%, preferably less than 10%.

According to specific embodiments of the invention, specific examples of compounds of formula (**I**), are reported in Table 1.

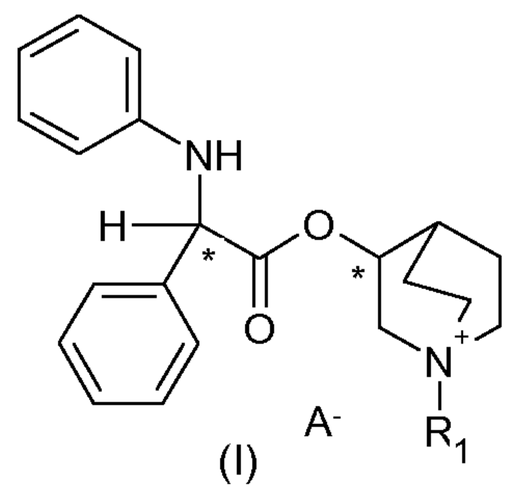
Table 1

Compound	Chemical name and structure
C1	(R)-1-(2-phenoxy-ethyl)-3-((R)-2-phenyl-2-phenylamino-acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
	
C2	(R)-1-(2-oxo-2-(thiophen-2-yl)ethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
	
C3	(R)-1-(3-phenoxypropyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
	
C4	(R)-1-methyl-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane trifluoroacetate
	

(continued)

C5	(R)-1-(2-oxo-2-phenylethyl)-3-(2-phenyl-2-(phenylamino)acetoxy)-1-azonia-bicyclo[2.2.2]octane chloride
	

The compounds of general formula (**I**) show at least two chiral centers that are represented by the carbon atoms quoted with asterisks.



(I)

Therefore, the formula (**I**) also encompasses any of the optical stereoisomers, diastereoisomers and mixtures thereof, in any proportion.

The formulation of the invention exhibits a good flowability, good uniformity of distribution of the active ingredient, and adequate chemical and physical stability in the device before use.

It also gives rise to a good respirable fraction and it is able of delivering an accurate therapeutically active dose of the active ingredient

The formulation of the invention comprises the active ingredient in an amount such that, upon administration by inhalation from inhalers, the therapeutically effective single dose (hereinafter the single dose) is advantageously comprised between 5 μg and 2500 μg, more advantageously between 10 μg and 2000 μg, preferably between 15 and 1000 μg, more preferably between 20 and 800 μg, even more preferably between 25 and 600 μg.

The single dose will depend on the kind and the severity of the disease

and the conditions (weight, sex, age) of the patient and shall be administered one or more times a day, preferably once or twice a day.

Without restricting the scope of the invention thereto, the pharmaceutical formulation may comprise any one of the compounds **C1** to **C5** in form of the above indicated salts, such that the administered single dose is comprised between 10 and 600 μg, preferably between 20 and 500 μg.

In a particular embodiment, the single dose may be comprised between 20 and 50 μg, while in other embodiments may be comprised between 40 mg and 100 μg or between 50 and 150 μg or between 100 and 300 μg, or between 300 and 500 μg.

In even more particular embodiments, the single dose may be of 20 or 25 or 50 or 100 or 200 or 500 μg.

If another salt were used, the single dose will vary on the basis of the different molecular weight of the counter ion.

The daily dose at which the pharmaceutical composition of the invention shall be comprised between 20 μg and 3000 μg, preferably between 40 μg and 1000 μg and more preferably between 50 μg and 500 μg.

In one embodiment, the daily dose may be reached by a single or double administration.

In another preferred embodiment, the daily dose may be reached by a single administration and delivered in one actuation of the inhaler.

In another preferred embodiment, the daily dose may be reached by a single administration and delivered in more actuations of the inhaler, preferably two.

In another preferred embodiment, the daily dose may be reached by a double administration and delivered in one actuation of the inhaler.

In another preferred embodiment, the daily dose may be reached by a double administration and delivered in more actuations of the inhaler,

preferably two.

The particles of a compound of formula (I) in the formulation of the invention must be in a finely divided (micronized) form, i.e. their mass median diameter should generally be equal to or less than 10 μm, preferably less than 6 μm, more preferably comprised between 1 and 6 μm.

In certain embodiments of the invention, the particle size may fulfill the following requirements:

i) no more than 10% of the particles have a mass diameter lower than 0.8 μm;

ii) no more than 50% of particles have a mass diameter lower than 1.7 micron, preferably comprise between 1.8 and 2.5 micron; and

iii) at least 90% of the particles have a mass diameter lower than 6 micron.

The active ingredient may be produced in the desired particle size using known methods, e.g. milling, direct precipitation, spray-drying, freeze-drying or supercritical fluids.

The carrier particles may be made of any physiologically acceptable pharmacologically- inert material or combination of materials suitable for inhalatory use.

For example, the carrier particles may be composed of one or more materials selected from sugar alcohols; polyols, for example sorbitol, mannitol and xylitol, and crystalline sugars, including monosaccharides and disaccharides; inorganic salts such as sodium chloride and calcium carbonate; organic salts such as sodium lactate; and other organic compounds such as urea, polysaccharides, for example starch and its derivatives; oligosaccharides, for example cyclodextrins and dextrins.

Advantageously, the carrier particles are made of a crystalline sugar, for example, a monosaccharide such as glucose or arabinose, or a disaccharide

such as maltose, saccharose, dextrose or lactose.

Preferably, the carrier particles are made of lactose, more preferably of α-lactose monohydrate.

In one embodiment the invention the powder formulation may be in form of agglomerated spheronized particles, also known as soft pellets, wherein the particles of a compound of general formula (I) and the particles of the carrier are both in a finely divided form, i.e. their mass median diameter is generally less than 10 micron, preferably from 1 to 6 micron.

Said kind of formulations may be prepared according to known methods.

Generally, the process comprises the steps of:

i) micronizing together the active ingredient and the carrier;

ii) subjecting the resulting co-micronized mixture to agglomeration and spheronisation.

Alternatively, the process comprises the following steps:

i) micronising separately the active ingredient and the carrier;

ii) mixing the micronized components; and

iii) subjecting the resulting mixture to agglomeration and spheronisation.

In another embodiment of the invention, the formulation comprises coarse particles of a carrier together with the drug in the finely divided form, a type of formulation known as ordered mixture.

Advantageously, said carrier coarse particles have a mass diameter (MD) of at least 50 micron, more advantageously greater that 80 micron Preferably, the MD is comprised between 90 micron and 500 micron.

In certain embodiments of the invention, the MD may be comprised between 90 and 150 micron.

In other embodiments, the MD may be comprised between 150 and

400 micron, with a MMD preferably greater than 175 micron, and more preferably the MD may be comprised between 210 and 355 micron.

The desired particle size may be obtained by sieving according to known methods.

When their MD is comprised between 150 and 400 micron, the carrier coarse particles have preferably a relatively highly fissured surface, that is, on which there are clefts and valleys and other recessed regions, referred to herein collectively as fissures.

The "relatively highly fissured" coarse particles can be defined in terms of fissure index or rugosity coefficient as described in WO 01/78695 and WO 01/78693, incorporated herein by reference, and they can be characterized according to the description therein reported.

Said carrier coarse particles may also be characterised in terms of tapped density or total intrusion volume measured as reported in WO 01/78695.

The tapped density of the carrier coarse particles is advantageously less than 0.8 g/cm^3, preferably between 0.8 and 0.5 g/cm^3.

The total intrusion volume is of at least 0.8 cm^3, preferably at least 0.9 cm^3.

When the formulation of the invention is in form of the aforementioned ordered mixture, it may advantageously comprise an additive material able to promote the release of the active particles from the carrier particles on actuation of the inhaler device, and hence able of improving the respirable fraction.

The additive material, which is preferably bound to the surface of the carrier coarse particles, is of a different material from the carrier particles.

Advantageously, the additive material is an amino acid, preferably selected from the group consisting of leucine, isoleucine, lysine, valine,

methionine, phenylalanine. The additive may be a salt of a derivative of an amino acid, for example aspartame or acesulfame K.

In one embodiment of the invention the additive particles consist substantially of leucine, advantageously L-leucine.

Alternatively, the additive material may include or consist of one or more water soluble surface active materials, for example lecithin, in particular soya lecithin.

In a particular embodiment of the invention, the additive material may include or consist of one or more lubricant selected from the group consisting of stearic acid and salts thereof such as magnesium stearate, sodium lauryl sulphate, sodium stearyl fumarate, stearyl alcohol, sucrose monopalmitate.

Other possible additive materials include talc, titanium dioxide, aluminium dioxide, and silicon dioxide.

Advantageously, the additive particles have a starting mean particle size of less than 35 micron. Preferably they have a mean particle size of not more than 15 micron, more preferably of not more than 10 micron.

The optimum amount of additive material shall depend on the chemical composition and other properties of the additive material.

In general, the amount of additive shall be not more than 10% by weight, based on the total weight of the formulation.

However, it is thought that for most additives the amount of additive material should be not more than 5%, preferably not more than 2% or even not more than 1% by weight or not more than 0.5% based on the total weight of the formulation. In general, the amount of additive material is of at least 0.01% by weight based on the total weight of the formulation.

In one of the preferred embodiment of the invention, the additive material is magnesium stearate.

The amount of magnesium stearate is generally comprised between

0.01 and 2%, preferably between 0.02 and 1%, more preferably between 0.1% and 0.5% by weight based on the total weight of the formulation.

In some embodiments, magnesium stearate may coat the surface of the carrier particles in such a way as that the extent of the molecular surface coating is at least of 5%, preferably more than 10%, more preferably more than 15%, even more preferably equal to or more than and 25%.

For very high extents of surface coating, i.e. higher than 60%, the coating may be achieved using the process described in the co-pending application EP 10158951.3.

The extent of molecular surface coating, which indicates the percentage of the total surface of the carrier particles coated by magnesium stearate, may be determined by water contact angle measurement as reported in WO 00/53157.

The extent to which the magnesium stearate coats the surface of the lactose particles can also be determined by scanning electron microscopy (SEM), versatile analytical technique well known in the art.

Such microscopy may be equipped with an EDX analyzer (an Electron Dispersive X- ray analyzer), that can produce an image selective to certain types of atoms, for example magnesium atoms. In this manner it is possible to obtain a clear data set on the distribution of magnesium stearate on the surface of carrier particles.

SEM may alternatively combined with IR or Raman spectroscopy for determining the extent of coating, according to known procedures.

Another analytical technique that can advantageously be used is X-ray photoelectron spectroscopy (XPS), by which it has been possible to calculate both the extent of coating and the depth of the magnesium stearate film around the lactose particles.

XPS measurements may be taken with commercially available

instruments such as Axis-Ultra instrument from Kratos Analytical (Manchester UK), typically using monochromated Al Kα radiation according to known procedures.

The formulations of the invention in the form of ordered mixture may also comprise fine particles of a physiologically acceptable pharmacologically- inert material with a mass median diameter (MMD) equal to or less than 15 micron, preferably equal to or less than 10 micron.

The percentage of fine particles of physiologically acceptable pharmacologically-inert material is advantageously comprised between 0.1 and 40% of the total amount of the formulation.

Preferably, the coarse particles and the fine particles are constituted of the same physiologically acceptable pharmacologically- inert material.

In a preferred embodiment of the invention, in particular when the single dose of the active ingredient is equal to or less than 300 μg, preferably equal to or less than 200 μg, the formulation is in form of hard-pellets according to the teaching of WO 01/78693.

Said formulation hence comprises:

i) particles of a compound of general formula (I) in a micronized form;

ii) a fraction of microparticles constituted of a mixture composed of particles of physiologically acceptable pharmacologically-inert material and particles of an additive material, said microparticles having a MMD equal to or less than 10 micron; and

iii) a fraction of particles of a physiologically acceptable pharmacologically-inert material having a highly fissured surface and a mass diameter (MD) comprised between 150 micron and 400 micron, preferably between 212 and 355 micron.

Advantageously the fraction of microparticles is composed of 90 to

99.5% by weight of the physiologically acceptable pharmacologically-inert material and 0.5 to 10% by weight of the additive material, and the ratio between the fraction of microparticles and the fraction of coarse particles is comprised between 1:99 and 40:60% by weight, preferably between 5:95 and 30:70% by weight, even more preferably between 10:90 and 20:80% by weight.

Preferably the physiologically acceptable inert material is α-lactose monohydrate and the additive material is magnesium stearate.

In a more preferred embodiment, the fraction of microparticles is composed of 98 to 99% by weight of α-lactose monohydrate and 1 to 2% by weight of magnesium stearate and the ratio between the fraction of microparticles and the fraction of coarse particles made of α-lactose monohydrate is 10:90% by weight, respectively.

The amount of magnesium stearate in the final formulation is advantageously comprised between 0.01 and 1.0% by weight, preferably between 0.05 and 0.5% by weight, more preferably between 0.1 and 0.4% by weight on the total weight of the formulation.

The formulation in form of ordered mixture according to the invention may be prepared according to known methods.

Sais methods comprise the step of mixing together the carrier coarse particles, the optional fine carrier particles and the additive particles, and finally adding the finely divided pharmaceutically active compound to the resulting mixture.

The particularly preferred formulation according to the invention may be prepared according to the methods reported in WO 01/78693.

Among the methods therein described, the formulation is preferably prepared according to a process which comprises the following steps:

a) preparing microparticles constituted of a mixture composed of

particles made of physiologically acceptable pharmacologically-inert material and particles of the additive, the inert material and the additive being first-mixed together and then co-micronised;

b) mixing the microparticles of step a) with coarse particles of a physiologically acceptable pharmacologically-inert material such that microparticles adhere to the surface of the coarse particles;

c) adding by mixing the active particles in the micronized form to the particles of step b).

The co-micronization step may be carried out by known methods such as those reported in WO 02/00197.

Advantageously, said step is carrier out by milling, more preferably by using a jet mill according to the conditions reported in WO 01/78693.

In a preferred embodiment, the microparticles of step a) obtained by co-micronization, are subjected to a conditioning step according to conditions disclosed in the co-pending application EP 10160565.7.

Advantageously, during the step a) the additive may be embedded in the formed microparticles, or alternatively, in the case of a lubricant such as magnesium stearate, the additive may coat the surface of the carrier particles in such a way as that the extent of molecular surface coating is at least of 5%, preferably more than 10%, more preferably more than 15%, even more preferably more than and 35%.

The extent of molecular surface coating indicates the percentage of the total surface of the carrier particles coated by magnesium stearate.

The presence of the additive material embedded in the microparticles may be detected according to known methods, for instance, by electron scanning microscope coupled to microcalorimetry.

On the contrary, as reported above, the extent of molecular surface coating may be determined by water contact angle measurement as reported in

WO 00/53157 or by other known tools.

The formulations of the invention may further comprise other therapeutic agents useful for the prevention and/or treatment of a respiratory disease, e.g. beta$_2$-agonists such as salmeterol, milveterol and vilanterol; corticosteroids such as fluticasone propionate or furoate, flunisolide, mometasone furoate, rofleponide and ciclesonide; phosphodiesterase-4 (PDE4) inhibitors such as roflumilast and combinations thereof.

The dry powder formulation herein described, may be used in all customary dry powder inhalers such as unit dose or multidose inhalers.

For example, the formulation of the invention may be filled in hard gelatine capsules, in turn loaded in a unit dose inhaler such as the Aerolizer^{TM}. Alternatively, the formulation as a powder may be filled in a multidose inhaler comprising a powder reservoir as described in WO 2004/012801.

Administration of the formulation of the invention may be indicated for prophylactic purposes or for symptomatic relief for a wide range of conditions including respiratory disorders such as chronic obstructive pulmonary disease (COPD) and asthma of all types. Other respiratory disorders for which the formulations of the invention may be beneficial are those characterized by obstruction of the peripheral airways as a result of inflammation and presence of mucus, such as chronic obstructive bronchiolitis, chronic bronchitis, emphysema, acute lung injury (ALI), cystic fibrosis, rhinitis, and adult or respiratory distress syndrome (ARDS).

In addition, the formulation of the invention may be useful in treating smooth muscle disorders such as urinary incontinence and irritable bowel syndrome; skin diseases such as psoriasis; hyperhydrosis and sialorrhea; and gastrointestinal ulcers.

The invention is better illustrated by the following examples.

EXAMPLES

Example 1 - Inhalable dry powder formulation comprising C1 (formulation 1)

A powder formulation according to the invention has the composition reported in Table 2:

Table 2

Components	*Amounts*		
	Per shot of the inhaler		Single dose
	mg	%	µg
C1	0.2	1.0	200
Alpha-lactose monohydrate 212-355 µm	17.82	89.1	
Co-micronised particles	1.98	9.9	
Total weight	20		

C1 is micronized by known methods, to prepare the active substance in the form of particles having a typical particle size suitable for inhalation.

The co-micronised particles are constituted of a mixture of α–lactose monohydrate and magnesium stearate in the ratio 98:2 w/w and are obtained by co-milling in a jet mill particles of α-lactose monohydrate having a mean particle size of less than 250 micron and magnesium stearate particles having a mean particle size of less than 35 micron.

The final formulation is filled in hard gelatine capsules and loaded in the Aerolizer^{TM} inhaler.

The aerosol performances are evaluated using a Multi Stage Liquid Impinger (MSLI) according to the procedure described in European Pharmacopoeia 2nd edition, 1995, part V.5.9.1, pages 15-17.

Example 2 - Inhalable dry powder formulation comprising C2 (formulation 2)

A powder formulation with a similar composition of that of Example 1, but using **C2**, is prepared.

The composition is reported in Table 3.

Table 3

Components	*Amounts*		
	Per shot of the inhaler		Single dose
	mg	%	µg
C2	0.2	1.0	200
Alpha-lactose monohydrate 212-355 µm	17.82	89.1	
Co-micronised particles	1.98	9.9	
Total weight	20		

The formulation is filled in hard gelatine capsules and loaded in the Aerolizer™ inhaler.

The aerosol performances are determined as reported in Example 1.

Example 3 - Inhalable dry powder formulation comprising C3 (formulation 3)

A further powder formulation according to the invention is prepared with the composition reported in Table 4.

Table 4

Components	*Amounts*		
	Per shot of the inhaler		Single dose
	mg	%	µg
C3	0.100	1.0	100
Alpha-lactose monohydrate 90-150 µm	8.91	89.1	
magnesium stearate	0.99	9.9	
Total weight	10		

The formulation is filled in the multidose dry powder inhaler described in WO 2004/012801.

Example 4 - Inhalable dry powder formulation comprising C4 (formulation 4)

A further powder formulation according to the invention is prepared with the composition reported in Table 5.

Table 5

Components	*Amounts*		
	Per shot of the inhaler		Single dose
	mg	%	µg
C4	0.200	2.0	200
Alpha-lactose monohydrate 90-150 µm	8.82	97.90	
magnesium stearate	0.98	0.10	
Total weight	10		

The formulation is filled in the multidose dry powder inhaler described in WO 2004/012801.

Example 5 - Inhalable dry powder formulation comprising C5 (formulation 5)

A powder formulation according to the invention was prepared as described in Example 1.

Its composition reported in Table 6:

Table 6

Components	*Amounts*		
	Per shot of the inhaler		Single dose
	mg	%	µg
C5	0.2	1.0	200
Alpha-lactose monohydrate 212-355 µm	17.82	89.1	
Co-micronised particles	1.98	9.9	
Total weight	20		

The final formulation was filled in hard gelatine capsules and loaded in the Aerolizer™ inhaler.

The aerosol performances were evaluated as reported in Example 1.

The results, as a mean of two determinations, in terms of delivered dose (DD), fine particle mass (FPM), fine particle fraction (FPF) and mass median aerodynamic diameter (MMAD), are reported in Table 7.

Table 7

DD µg	FPM µg	FPF %	MMAD µm
61.1	39.8	65.0	2.2

The FPF turned out to be excellent, indicating that said kind of formulation is capable of providing good aerosol performances.

Example 6 – Further inhalable dry powder formulations comprising C5

Powder formulations with a similar composition of that of Example 5 are prepared using different strengths of **C5** and different percentages of co-micronized particles.

The compositions are reported in Table 8 and 9.

Table 8

Strenght	**10 µg/ 10 mg**	**10 µg/ 10 mg**	**100 µg/ 10 mg**	**200 µg/ 10 mg**
α-lactose monohydrate 212-355 µm (mg)	8.991	8.4915	8.415	8.82
α-lactose monohydrate 212-355 µm (%)	89.9	84.9	84.0	88.0
Co-micronized particles (mg)	0.999	1.4985	1.485	0.98
Co-micronized particles (%)	10	15	15	10
C5 (mg)	0.010	0.010	0.100	0.200
C5 (%)	0.1	0.1	1	2.0
Total	10 mg	10 mg	10 mg	10 mg

The formulation is filled in the multidose dry powder inhaler described

in WO 2004/012801.

Table 9

Strenght	**20 µg/ 20 mg**	**20 µg/ 20 mg**	**200 µg/ 20 mg**
α-lactose monohydrate 212-355 µm (mg)	17.982	16.803	16.83
α-lactose monohydrate 212-355 µm (%)	89.9	84.9	84.0
Co-micronized particles (mg)	1.998	2.997	2.97
Co-micronized particles (%)	10	15	15
C5 (mg)	0.020	0.020	0.200
C5 (%)	0.1	0.1	1.0
Total	20 mg	20 mg	20 mg

The formulation is filled in hard gelatine capsules and loaded in the Aerolizer™ inhaler.

Example 7 - Assessment of the bronchodilation activity of the compounds of the invention

Airway reactivity is measured using barometric plethysmography (Buxco, USA). Male guinea pigs (500-600 g) are individually placed in plexiglass chambers. After an acclimatisation period, animals are exposed to nebulised saline for 1 min to obtain airway baseline reading. This is followed by a 1 min challenge with nebulised acetylcholine (Ach) -2.5 mg/mL.

After 60 min, 5 min nebulisation of vehicle or the preferred compounds of the invention in the range 0.1 -1 mM are applied and Ach challenge is then repeated after 2, 5, 24, 48 and 72 hours (h). Recording of pressure fluctuations in the chambers are taken for 5 min after each nebulisation and analysed to

calculate Enhanced Pause (Penh). Airway reactivity is expressed as percentage increase in Penh compared with Penh values from the nebulisation of vehicle.

Two hours after the end of nebulisation, the Ach-induced increase in Penh is dose-dependently inhibited by the compounds, with a maximal effect at around 1 mM.

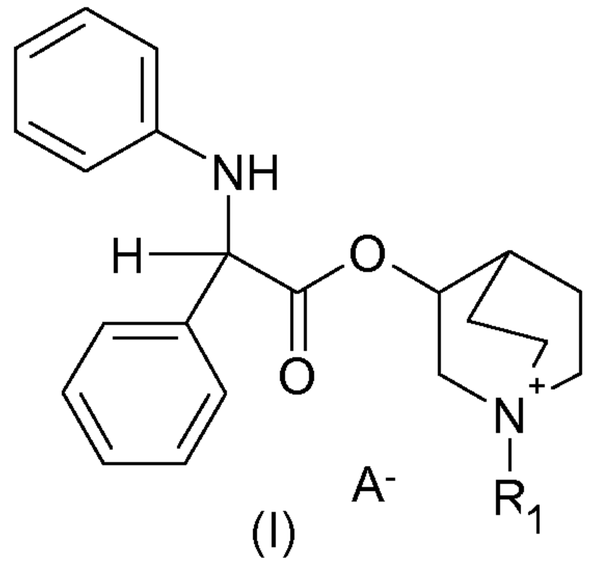
As for the time-course of the effect, said compounds show an increasing duration of action with increasing dose.

After inhalation of 0.1 mM of said compounds, the effect persisted significantly up to 24 h.

The estimation of lung levels for said compounds achieved after nebulisation of a dose endowed with a submaximal bronchodilator activity at 2 h after treatment reveals that the their retained dose in the target organ is less than 5 μg/kg. If an extrapolation of these results from guinea pig to human is made, it can be predicted that in patients the daily dose might be comprised between 20 and 500 μg.

CLAIMS

1. An inhalable dry powder formulation comprising, as active ingredient, micronized particles of a compound of general formula (**I**)



(I)

wherein:

$\mathbf{R_1}$ is a group of formula **(Y)**

---(CH_2)p---P---W

(Y)

wherein

p is 0 or an integer from 1 to 4;

P is absent or is selected from the group consisting of O, S, SO, SO_2 and CO;

W is selected from the group consisting of H, aryl and heteroaryl, wherein aryl and heteroaryl are optionally substituted by one or more substituents selected from the group consisting of halogen atoms, OH, SH, NO_2, CN, COOH and NH_2;

A^- represents a physiologically acceptable anion;

and particles of a physiologically acceptable pharmacologically-inert solid carrier.

2. The inhalable powder according to claim 1, wherein the physiologically acceptable anion A^- is selected from the group consisting of chloride, bromide,

iodide, trifluoroacetate, formate, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulfonate.

3. The inhalable powder according to claim 1 or 2, wherein the active ingredient is administered at a single dose comprised between 5 µg and 2500 µg.

4. The inhalable powder according to claim 3, wherein the single dose is comprised between 10 µg and 2000 µg.

5. The inhalable powder according to claim 4, wherein the single dose is comprised between 15 µg and 1000 µg.

6. The inhalable powder according to claim 5, wherein the single dose is comprised between 20 µg and 800 µg.

7. The inhalable powder according to claim 6, wherein the single dose is comprised between 25 and 600 µg.

8. The inhalable powder according to any one of claims 1 to 7, wherein the carrier comprises a crystalline sugar selected from the group consisting of glucose, arabinose, maltose, saccharose, dextrose and lactose or a polyalcohol selected from the group consisting of mannitol, maltitol, lactitol and sorbitol.

9. The inhalable powder according to claim 8, wherein the sugar is lactose.

10. The inhalable powder according to claim 9, wherein the sugar is α-lactose monohydrate.

11. The inhalable powder according to any one of claims 1 to 10, wherein the carrier is in form of finely divided particles having a mass median diameter (MMD) equal to or of less than 10 micron.

12. The inhalable powder according to any one of the claims 1 to 10, wherein the carrier is in form of coarse particles having a mass diameter of at least 50 micron.

13. The inhalable powder according to claim 12, wherein the mass diameter is comprised between 150 and 400 micron.

14. The inhalable powder according to any one of claims 1 to 10, wherein the carrier comprises a mixture of coarse particles having a mass diameter comprised between 150 and 400 micron and finely divided particles with a MMD equal to or less than 10 micron.

15. The inhalable powder according to any one of claims 11 to 14, further comprising one or more additive materials selected form the group consisting of amino acids, water soluble surface active agents, lubricants and glidants.

16. The inhalable powder according to claim 15, wherein the additive material is a lubricant.

17. The inhalable powder according to claim 16, wherein the additive material is magnesium stearate.

18. The inhalable powder according to claim 17, wherein magnesium stearate is present in an amount comprised 0.01 and 2% by weight based on the total weight of the formulation.

19. The inhalable powder according to claim 18, wherein the amount of magnesium stearate is comprised between 0.02 and 1% w/w.

20. A dry powder inhaler comprising an inhalable dry powder formulation according to any one of claims 1 to 19.

21. The inhalable dry powder formulation according to any one of claims 1 to 19, for use for the prevention and/or treatment of any disease wherein inhibition of the muscarinic receptor is required.

22. The inhalable powder according to claim 21, wherein the disease is respiratory disease such as asthma and chronic obstructive pulmonary disease (COPD).

23. A package comprising an inhalable dry powder formulation according to any one of claims 1 to 19 and a dry powder inhaler.