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(57) Abrégé/Abstract:
The invention relates to a pharmaceutical formulation to be administered by pressurized metered dose inhalers (pMDIs), comprising a compound of general formula (I). The invention also relates to the process for the preparation and to a pressurized metered dose inhaler filled with said pharmaceutical formulation.

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(54) Title: PHARMACEUTICAL FORMULATION COMPRISING A PHOSPHODIESTERASE INHIBITOR

(57) Abstract: The invention relates to a pharmaceutical formulation to be administered by pressurized metered dose inhalers (pMDIs), comprising a compound of general formula (I). The invention also relates to the process for the preparation and to a pressurized metered dose inhaler filled with said pharmaceutical formulation.

PHARMACEUTICAL FORMULATION COMPRISING A PHOSPHODIESTERASE INHIBITOR

FIELD OF THE INVENTION

The invention relates to a pharmaceutical formulation to be administered by pressurized metered dose inhalers (pMDIs) or nebulizers, comprising a compound of general formula (I).

The invention also relates to the process for the preparation and to a pressurized metered dose inhaler or single or multidose dose vials for nebulizer filled with said pharmaceutical formulation.

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.

Inhaled corticosteroids are the current maintenance therapy of choice for asthma and together with bronchodilator β_2-agonists for acute symptom relief, they form the mainstay of current therapy for the disease. The current management of COPD is largely symptomatic by means of bronchodilating therapy with inhaled anticholinergics and inhaled β_2-adrenoceptor agonists. However, corticosteroids do not reduce the inflammatory response in COPD as they do in asthma.

Another class of therapeutic agents which are under investigation in

view of its anti-inflammatory effects for the treatment of inflammatory respiratory diseases such as asthma and COPD is represented by the inhibitors of the phosphodiesterase enzymes (PDEs), in particular of the phosphodiesterase type 4 (hereinafter referred to as PDE4).

Various compounds acting as PDE4 inhibitors have been disclosed. However, the usefulness of several PDE4 inhibitors of the first -generation such as rolipram and piclamilast has been limited because of their undesirable side effects such as nausea, gastric acid secretion and emesis due to their action on PDE4 in the central nervous system and due to the action on PDE4 in parietal cells in the gut.

The cause of said side effects has been widely investigated.

It has been found that PDE4 exists in two distinct forms representing different conformations, that were designated as high affinity rolipram binding site or HPDE4, especially present in the central nervous system and in parietal cells, and low affinity rolipram binding site or LPDE4 (Jacobitz, S et al Mol. Pharmacol, 1996, 50, 891-899), which is found in the immune and inflammatory cells. While both forms appear to exhibit catalytic activity, they differ with respect to their sensitivity to inhibitors. In particular, compounds with higher affinity for LPDE4 appear less prone to induce side-effects such as nausea, emesis and increased gastric secretion.

The effort of targeting LPDE4 has resulted in a slight improvement in the selectivity for the second-generation PDE4 inhibitors such as cilomilast and roflumilast. However, even these compounds are not provided with a good selectivity towards LPDE4.

Compounds with selective LPDE4 inhibition activity are disclosed in WO 2009/018909.

Additional PDE4 inhibitors having high potency are object of the co-pending application n. PCT/EP2010/000676, wherein it has been surprisingly

found that the presence of sulphonamido substituents on the benzoate residue markedly improves the potency and that the (-) enantiomers are more potent than the corresponding (+) enantiomers and racemates.

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

The aim of the present invention is to provide a hydrofluoroalkane (HFA) based pressurized metered dose inhaler (pMDI) aerosol composition that comprises a compound of general formula (I) acting as PDE4 inhibitor, as active ingredient.

The aim of the present invention is also to provide a propellant-free composition for nebulisation, comprising a compound of general formula (I) acting as PDE4 inhibitor, to be administered by suitable devices.

The aim of the present invention is also to obtain a chemically and physically stable aerosol formulation for inhalation of a PDE4 in form of pMDI or formulation for nebulisation.

SUMMARY OF THE INVENTION

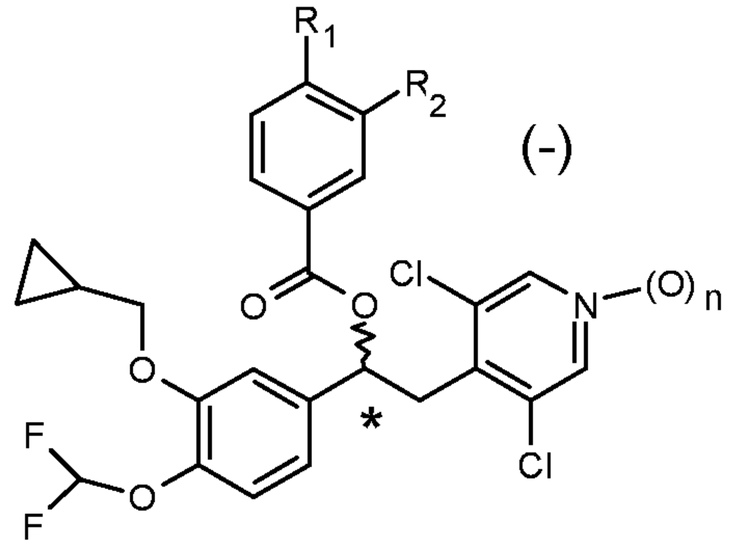
The invention relates to a pharmaceutical suspension formulation to be administered by pressurized metered dose inhalers (pMDIs) comprising particles of a micronized crystalline compound of general formula (I) and a propellant.

The invention also relates to the process for the preparation and to a pressurized metered dose inhaler filled with said pharmaceutical formulation.

The present invention also provides a liquid, propellant-free pharmaceutical formulation for administration by nebulisation, comprising a compound of general formula (I), dissolved or suspended in water, optionally in presence of one or more co-solvents.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a pharmaceutical formulation to be administered by pressurized metered dose inhalers (pMDIs) or nebulizers, comprising a compound of general formula (I) as (-) enantiomers, represented by the following general formula (I)



(I)

wherein:

n is 0 or 1;

R_1 and R_2 may be the same or different, and are selected from the group consisting of:

- linear or branched (C_1-C_6)alkyl, optionally substituted by one or more halogen atoms;
- OR_3 wherein R_3 is a linear or branched (C_1-C_6)alkyl optionally substituted with one or more halogen atoms or (C_3-C_7)cycloalkyl groups; and
- $HNSO_2R_4$ wherein R_4 is a linear or branched (C_1-C_4)alkyl optionally substituted with one or more halogen atoms,

wherein at least one of R_1 and R_2 is $HNSO_2R_4$.

Preferably, the (-) enantiomers are used in a substantially pure form.

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

The expressions "% w/w" and "% w/v" mean the weight percentage of the component with respect to the total weight or the total volume of the composition, respectively. By "anhydrous ethanol" it is meant a content of ethanol of not less than 99.5% V/V.

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

When administered by pMDIs, said daily dose may be delivered in one or more actuations, preferably one actuation (shot) of the inhaler.

For "actuation" it is meant the release of the active ingredient from the device by a single activation (e.g. mechanical or breath).

The term "substantially pure" means an active ingredient having an optical purity higher than 95% w/w, preferably higher than 98% w/w.

The term "mass median diameter" means the median diameter which divides the mass of particles in two equal parts.

The term "delivered dose" (DD) is calculated from the cumulative deposition in the Andersen Cascade Impactor (ACI) or Next Generation Impactor (NGI) stages, divided by the number of actuations per experiment.

The term "fine particle mass" (FPM) means the total mass of delivered drug recovered on the ACI or NGI stages that capture particles in the respirable particle range (aerodynamic diameter <5 μm). The aerodynamic diameter is a physical property of a particle in a viscous fluid such as air. In general, particles have irregular shapes with actual geometric diameter that are difficult to measure. Aerodynamic diameter is an expression of a particle's aerodynamic behavior as if it were a perfect sphere with unit-density and diameter equal to the aerodynamic diameter.

The term "fine particle fraction" (FPF) means the percent ratio between the respirable dose and the delivered dose.

The expression “chemically stable formulation” means a formulation wherein the stability and the shelf-life of the active ingredient meet the requirements of the ICH Guideline Q1B, relevant for drug product stability testing for the purposes of drug registration.

In the context of the suspension formulations, the expression “physically stable” refers to formulations which exhibit substantially no growth in particle size or change in crystal morphology of the active ingredient over a prolonged period, are readily redispersible, and upon redispersion, do not flocculate so quickly as to prevent reproducing dosing of the active ingredient.

The term “ready-to-use preparation for administration by nebulisation” refers to a preparation which is administered directly without further handling and is dispersed in air to form an aerosol by means of a nebulizer, e.g. an instrument that is capable of generating very fine liquid droplet for inhalation into the lungs.

In one aspect, the present invention provides a pharmaceutical formulation suitable for aerosol administration by a pMDI, now defined pMDI formulation, comprising a compound of general formula (I) and a propellant.

In a particular embodiment, said pMDI formulation may be in form of suspension of particles of a micronized crystalline compound of general formula (I) in said propellant, so as to permit inhalation of the active ingredient into the lungs upon administration of the aerosol formulation.

Advantageously the particles of the active ingredient shall have a mass median diameter (MMD) of less than 10 micron, preferably in the range of 1 to 10 micron, more preferably between 1 and 6 microns.

Any pressure-liquefied propellant may be used, preferably a hydrofluoroalkane (HFA) propellant. Examples of HFA propellants include 1,1,1,2-tetrafluoroethane (HFA134a), 1,1,1,2,3,3,3-heptafluoro-propane

(HFA227) and mixtures thereof.

In certain embodiments the propellant may consist of HFA 134a, while in other embodiments, the propellant may consist of HFA 227 or a mixture thereof in any ratio.

In a particular embodiment the suspension pMDI formulations may comprise a surfactant, which may also act as a valve lubricant.

Suitable surfactants are known in the art and include: sorbitan esters such as sorbitan trioleate, sorbitan monolaurate, sorbitan mono-oleate and their ethoxylated derivates such as polysorbate 20, polysorbate 80; ethylene oxide/propylene oxide co-polymers and other agents such as natural or synthetic lecithin, oleic acid, polyvinylpyrrolidone (PVP), preferably PVP (K25) and polyvinyl alcohol, olive oil, glyceryl monolaurate, corn oil, cotton seed oil or sunflower seed oil, isopropyl myristate, oleyl alcohol, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan mono-oleate, oleyl polyoxyethylene (2) ether, stearyl polyoxyethylene (2) ether, lauryl polyoxyethylene (4) ether, block copolymers of oxyethylene and oxypropylene, diethylene glycol dioleate, tetrahydrofurfuryl oleate, ethyl oleate, glyceryl mono-oleate, glyceryl monostearate, glyceryl monoricinoleate, cetyl alcohol, stearyl alcohol, cetyl pyridinium chloride, ethylene oxide/propylene oxide co-polymer and ethoxylated alcohols such as polyethylene glycol (PEG) 300-1000, diethylene glycol monoethyl ether, Antarox and Brij.

In a preferred embodiment, the surfactant is PEG 600 or PVP (K25) or a mixture thereof.

The amount of surfactant, which may be present in the pMDI formulation according to the invention, is usually in the range of 0.001 to 3.0% (w/w), preferably between 0.005 to 1.0% (w/w).

In a preferred embodiment of the invention, the pMDI formulation may

contain a co-solvent.

Said co-solvent includes, but it is not limited to, polar compounds that contain one or more hydroxyl groups or other polar groups. For example, it includes: an alcohol, such as ethanol, preferably anhydrous ethanol, isopropanol; a glycol such as propylene glycol, polyethylene glycol, polypropylene glycol or glycerol; a glycol ether; and a polyoxyethylene alcohol.

Preferably anhydrous ethanol is used in a concentration lower than 20% (w/w), more preferably below 15%, even more preferably between 1% and 5% (w/w), most preferably 1 or 5% (w/w).

In other embodiments, the pMDI formulations according to the invention, may additionally comprise further excipients. Examples of excipients are sugars such as lactose, amino acids such as alanine, betaine, cysteine, and/or antioxidants such as ascorbic acid, citric acid, sodium edetate, editic acid, tocopherols, butylhydroxytoluene, butylhydroxyanisol and ascorbyl palmitate.

The weight ratio of the drug to the excipient is generally in the range from 1:0.1 to 1:100.

The pharmaceutical pMDI formulation of the invention may contain at least an active compound selected from the group consisting of **C1, C2, C3, C4, C5** and **C6**, in an amount comprised between 0.02 and 0.7% w/w, preferably between 0.05 and 0.5%, anhydrous ethanol in an amount from between 1 to 5% w/w, one or more surfactant in an amount from 0.001% to 3% w/w. The propellant is HFA134a or HFA227 or a mixture thereof.

To prepare the suspension pMDI formulation according to the invention, the crystalline compound selected from the group consisting of **C1, C2, C3, C4, C5** and **C6**, is obtained as reported in the co-pending patent application no. PCT/EP2010/000676, is micronized by methods known *per se*

in the art, to prepare the active substance in the form of particles having a typical particle size suitable for inhalation, < 3 μm.

According to another aspect, the present invention provides a pMDI comprising a canister filled with the pharmaceutical formulation of the invention and a metering valve for delivering a daily therapeutically effective dose of the active ingredient.

The pMDI formulation of the invention shall be filled into pMDIs.

Said pMDIs comprise a canister fitted with a metering valve. Actuation of the metering valve allows a small portion of the spray product to be released.

Part or all of the internal surfaces of the canister may be made of glass or of a metal, for example aluminum or stainless steel or anodized aluminum.

Alternatively the metal canister may have part or all of the internal surfaces lined with an inert organic coating. Examples of preferred coatings are epoxy-phenol resins, perfluorinated polymers such as perfluoroalkoxyalkanes, perfluoroalkoxyalkylenes, perfluoroalkylenes such as poly-tetrafluoroethylene (Teflon), fluorinated-ethylene-propylene, polyether sulfone and fluorinated–ethylene-propylene polyether sulfone (FEP-PES) mixtures or combination thereof. Other suitable coatings could be polyamide, polyimide, polyamideimide, polyphenylene sulfide or their combinations.

In certain embodiments canisters having the internal surface lined with Teflon may preferably be used.

In other particular embodiments canisters made of stainless steel may preferably be used.

The canister is closed with a metering valve for delivering a daily therapeutically effective dose of the active ingredient.

Generally the metering valve assembly comprises a ferrule having an aperture formed therein, a body molding attached to the ferrule which houses

the metering chamber, a stem constituted of a core and a core extension, an inner- and an outer seal around the metering chamber, a spring around the core, and a gasket to prevent leakage of propellant through the valve.

The gasket may comprise any suitable elastomeric material such as, for example, low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber, neoprene, EPDM (a polymer of ethylenepropylenediene monomer) and TPE (thermoplastic elastomer). EPDM rubbers are particularly preferred.

Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France, Bespak, plc UK and 3M, Neotechnic Ltd UK.

In general terms the valve seals, especially the gasket seal, as well as the seals shall preferably be manufactured of a material which is inert to and resists extraction into the contents of the formulation, especially when the contents include ethanol.

Advantageously the material of the metering chamber is inert to and may resist distortion by contents of the formulation. Particularly suitable materials for use in manufacture of the metering chamber include acetals and polyesters e.g. polybutyleneterephthalate (PBT).

According to a preferred embodiment of the invention the material of all the internal surface of the canister as well as the material of the metering chamber, the core, the core extension, the spring and the body of the valve may be substantially or completely made of a metal, preferably of stainless steel.

Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (eg. DF10, DF30, DF31, DF60), Bespak pic, UK (eg. BK300, BK356, BK357) and 3M-Neotechnic Ltd, UK (eg. Spraymiser).

The formulation shall be actuated by a metering valve able of delivering a volume of between 25 µl and 100 µl, e.g. 25 µl, 63 µl or 100 µl.

Advantageously the MDI device filled with the formulation may be equipped with a dose counter.

Conventional bulk manufacturing methods and known machinery may be employed for the preparation of large scale batches for the commercial production of filled canisters.

For example, the pMDI suspension formulations according to the invention may be prepared by adding the active ingredient to a chilled propellant or optionally a pre-mixed blend of propellant and optionally further excipients and, then dispersing the resulting suspension using a suitable mixer. After homogenization the suspension can be filled into the MDI canister which is closed by crimping a metering valve on the canister.

Alternatively the active ingredient and optionally further excipients can be added to a vessel. The liquefied propellant is then introduced into the vessel under pressure and the active ingredient is dispersed and homogenized using a suitable mixer and homogenizer. After homogenization the bulk formulation can be transferred into the individual MDI canisters by using valve to valve transfer methods.

Alternatively, the co-solvent, if it is present, is introduced into a vessel at room pressure. The active ingredient and optional further excipients are added and homogenised using a suitable homogenizer. The ethanolic suspension is kept under stirring. The ethanolic bulk is then dosed into the open canister. The valve is placed onto the can and crimped. Finally, the canister is pressure-filled with the final solution formulation through the valve.

The pMDI formulations according to the invention, depending on volume of the metering valve to be used, may suitably comprise from 0.1 mg

to 80 mg of a compound of formula (I) per ml, preferably from 0.5 mg to 25 mg per ml.

The pMDI formulations in the form of suspensions comprising particles of a micronized crystalline compound of general formula (I) and a propellant, comprise the active ingredient in an amount such that, in case of administration by inhalation from inhalers, the daily therapeutically effective dose (hereinafter the daily dose) of compound of formula (I) is advantageously comprised between 10 µg and 2000 µg, preferably between 20 µg and 1000 µg, even more preferably between 50 µg and 800 µg, even more preferably between 80 and 700 µg, even more preferably between 300 µg and 600 µg.

According to a preferred embodiment, the single dose may be comprised between 100 and 300 µg, while according to another preferred embodiment, the single dose may be comprised between 200 and 800 µg, more preferably between 300 and 600 µg.

In further embodiments, the single dose may be 100 µg, 200 µg or 400 µg or 600 µg.

Said dose will depend on the kind and the severity of the disease and the conditions (weight, sex, age) of the patient and will be administered one or more times a day, preferably once a day.

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 daily dose may be delivered in one or two or more actuations (shots) of the inhaler wherein the pharmaceutical composition is contained. For example, a 400 μg daily dose may be administered in one shot of 400 μg or as two shots of 200 μg dose.

In another aspect, the compound of general formula (I) may be dissolved or suspended, to give a nebulised aqueous solution or suspension, now defined nebulised formulation, available either as for a single dose or multi-dose vials formulation.

Said nebulised formulation may have the pH and/or tonicity adjusted with suitable buffers and/or isotonic agents, and optionally, it could also comprise stabilizing and/or preserving agents.

In a more preferred embodiment, said nebulised formulation may comprise a solvent.

In a preferred embodiment, said nebulised formulation may comprise a solvent selected from water or an aqueous solution and a water-miscible co-solvent.

Said co-solvent includes, but it is not limited to polar compounds that contain one or more hydroxyl groups or other polar groups. For example, it includes alcohols, such as ethanol, anhydrous ethanol, isopropanol and glycols including propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol and polyoxyethylene alcohols.

The present invention also provides a single dose or multidose vial filled with said nebulised formulation for delivering a daily therapeutically dose of the active ingredient by a nebulizer.

The liquid, propellant-free pharmaceutical formulation in the form of ready-to-use preparation for administration by nebulisation of the invention, comprise compound of formula (I) in an amount such that the daily dose is advantageously comprised between about 35 μg and about 7000, preferably between about 70 μg and about 3500 μg, even more preferably between about 175 μg and about 2800 μg, even more preferably between about 280 μg and about 2100 μg, even more preferably between about 350 μg and about 1750 μg.

According to a preferred embodiment, the single dose may be comprised between about 350 and about 700 μg, while according to another preferred embodiment, the single dose may be comprised between about 700 and about 1400 μg.

In further embodiments, the single dose may be about 350 μg, about 700 μg or 1400 μg.

The formulation is preferably used as ready-to-use formulation.

However said nebulised formulations may also be realized in a lyophilised form in unitary doses for the reconstitution in a solution. In this alternative embodiment a single dose of a lyophilised preparation may be reconstituted before use with a solvent vial in a solution.

These nebulised formulations may also be distributed in suitable containers such as multidose vials or, preferably, single dose vials for single dosage administration. Said single-dose vials may be pre-sterilised or, preferably, may be aseptically filled using the "blow, fill and seal" technology. The filling is preferably carried out under inert atmosphere.

Solution formulations can be advantageously sterilized by filtration. The single-dose vials are preferably of 2 ml. For suspension formulations, the sterilization process is carried out through known techniques.

These formulations are intended for administration using suitable

nebulizing apparatus such as jet nebulizers, ultrasonic nebulizers, mesh-vibrating nebulizers, soft-mist nebulizers such as Respimat® or others.

Therefore the invention is also directed to a kit comprising the nebulised formulation provided herein filled in vials for single dosage administration and a nebulizer.

According to a preferred embodiment, the pMDI and nebulized formulations of the invention comprise a compound of general formula (I), selected from **C1, C2, C3, C4, C5 and C6**, reported below:

Compound	**Chemical name**
C1	(-)-3-Cyclopropylmethoxy-4-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-pyridin-4-yl)-ethyl ester
C2	(-)-3-Cyclopropylmethoxy-4-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethyl ester
C3	(-)-4-Cyclopropylmethoxy-3-methanesulfonylamino-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethyl ester
C4	(-)-3,4-Bis-methanesulfonylamino-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethyl ester
C5	(-)-3-Methanesulfonylamino-4-methyl-benzoic acid 1-(3-cyclopropyl-methoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethyl ester
C6	(-)-4-Methanesulfonylamino-3-methyl-benzoic acid 1-(3-cyclopropylmethoxy-4-difluoromethoxy-phenyl)-2-(3,5-dichloro-1-oxy-pyridin-4-yl)-ethyl ester

In an embodiment, the preferred compound of the pMDI formulation or nebulized formulation is **C1.** In another one is **C2**. In further preferred embodiments, the compound might be **C3, C4**, **C5** or **C6**.

All the pMDI and nebulized formulations of the invention may further comprise other therapeutic agents currently used in the treatment of respiratory disorders, e.g. corticosteroids such as triamcinolone acetonide, fluticasone propionate, fluticasone furoate, flunisolide, mometasone furoate, rofleponide and ciclesonide; anticholinergic or antimuscarinic agents such as ipratropium bromide, oxytropium bromide, glycopyrronium bromide and tiotropium bromide; long-acting β_2 agonist such as vilanterol, indacaterol, milveterol, salbutamol, levalbuterol, terbutaline, AZD-3199, BI-1744-CL, LAS-100977, bambuterol, isoproterenol, procaterol, clenbuterol, reproterol, fenoterol and ASF-1020 and salts thereof.

The invention also relates to any one of the formulations described before, for use as a medicament.

In a further aspect, the present invention comprises any one of the formulations described before, for use in the prevention and/or treatment of an inflammatory or obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD).

In a further aspect, the present invention comprises the use of any one of the formulations described before, in the prevention and/or treatment of an inflammatory or obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD).

In a still further aspect, the present invention comprises 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 one of the formulations described before.

Administration of all the formulations of the invention may be indicated for the prevention and/or treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Other respiratory disorders characterized by obstruction of the peripheral airways as a result of inflammation and presence of mucus such as chronic obstructive bronchiolitis and chronic bronchitis may also benefit by this kind of formulation.

The invention is better illustrated by the following examples.

Example 1

A pharmaceutical aerosol composition was prepared, comprising C2, anhydrous ethanol as co-solvent, PVP (K25) as surfactant and HFA227 propellant, as reported in Table 1.

Table 1

Component	µg/actuation	Quantity
C2	200	0.23% w/w
Anhydrous ethanol	857	1.0% w/w
PVP (K25)	86	0.1% w/w
HFA 227	84538	98.67% w/w
Total	85681	100% w/w

The efficacy of an MDI device is a function of the dose deposited at the appropriate site in the lungs. Deposition is affected by the aerodynamic particle size distribution of the formulation which may be characterised in vitro through several parameters.

The aerodynamic particle size distribution of the formulation of the invention may be characterized using a Cascade Impactor according to the procedure described in the European Pharmacopoeia 6th edition, 2009 (6.5), part 2.09.18. An Apparatus E, operating at a flow rate range of 30 l/min to

100 l/min or an Apparatus D ACI, operating at a flow rate of 28.3 l/min. Deposition of the drug on each ACI plate is determined by high performance liquid chromatography (HPLC).

The following parameters of the particles emitted by a pressurized MDI may be determined:

i) mass median aerodynamic diameter (MMAD) is the diameter around which the mass aerodynamic diameters of the emitted particles are distributed equally;

ii) delivered dose is calculated from the cumulative deposition in the ACI, divided by the number of actuations per experiment;

iii) respirable dose (fine particle dose = FPD) is obtained from the deposition from Stages 3 (S3) to filter (AF) of the ACI, corresponding to particles of diameter $\leq$ 4.7 microns, divided by the number of actuations per experiment;

iv) respirable fraction (fine particle fraction=FPF) which is the percent ratio between the respirable dose and the delivered dose.

Physical and chemical stability of the formulation reported in table 1 has been assessed in a stability study at 1 and 3 months at 25°C/60% relative humidity (RH).

Performances of the formulation reported in Table 1 were characterized using NGI.

Chemical stability and performances data of the formulation are reported in table 2, wherein “mean delivered dose intra-can” means the mean delivered dose of ten actuations on the same can (3 actuations at the beginning, 4 actuations in the middle and 3 actuations at the end of the life of the can).

Table 2

Test	Check points		
	T=0	1 month at 25°C/60%RH	3 months at 25°C/60%RH
C2 Can content (%)	100	101.1	100.6
Total impurities/Degradation products (%)	1.5	1.7	1.5
FPM (µg)	118.7	128.4	128.2
FPF (%)	79.3	81.4	81.3
MMAD (µm)	2.4	2.5	2.5
Mean delivered dose intra-can (µg)	149.72	156.88	157.7
Uniformity of Delivered Dose intra-can	Complies with the requirement of Ph.Eur.	Complies with the requirement of Ph.Eur.	Complies with the requirement of Ph.Eur.

*NGI sampling flow rate=30 l/min

Data reported in table 2 shows a good chemical stability of C2 (no degradation during stability). The formulation showed good delivered dose uniformity and a high fine particle fraction.

Physical stability of the formulation reported in table 1 was assessed using Turbiscan® Lab Expert equipment for a time period of 10 minutes.

Turbiscan enables to get a quick and objective measurement of the sedimentation behavior of suspension drugs and it is therefore preferred with respect to visual observation.

The different instability phenomena (creaming, sedimentation, flocculation, coalescence) can be identified and quantified via different parameters, allowing an objective analysis to be made.

The heart of the optical scanning analyzer, Turbiscan®, is a detection head, which moves up and down along a flat-bottom cylindrical glass cell. The

detection head is composed of a pulsed near infrared light source (λ = 880 nm) and two synchronous detectors.

Turbiscan can be used in two different modes: backscattering mode or transmission mode. Turbiscan has been used in the reported examples in transmission mode, i.e. to measure the transmitted light as a function of time.

For pressurized systems a cell capable of handling pressurized samples is required. Such a cell was used for the evaluations of these HFA formulations.

Delta T is the parameter used for the physical characterization of the formulations reported in the examples. Delta T measure the % of variation of light Trasmitted through the sample in a predetermined range of time. In particular for the examples here reported Delta T was measured for a time period of 10 minutes, time window that widely cover the time needed for patient to use the device. Physically stable suspension has a low value of this parameter (<1%) whilst for unstable suspension this percentage increase significantly.

Delta T for the formulation reported in table 1, after 10 minutes, is less than 0.2%, confirming its physical stability.

Example 2

A pharmaceutical aerosol composition was prepared, comprising C2, anhydrous ethanol as co-solvent, PVP (K25) as surfactant and HFA227 propellant, as reported in Table 3:

Table 3

COMPONENT	µg/actuation	Quantity
C2	200	0.23%w/w
Anhydrous ethanol	4284	5%w/w
PVP (K25)	85.68	0.1%w/w
HFA 227	81111	94.67%w/w
Total	85681	100% w/w

Performances of the formulation reported in Table 3 were characterized using NGI. Data are reported in Table 4:

Table 4

Delivered Dose [µg]	Fine Particle Mass [µg]	Fine particle Fraction [%]	MMAD [µm]
161.76	64.23	39.9	3.2

*NGI sampling flow rate=30 l/min

Delta T for the formulation reported in table 3, after 10 minutes, is less than 0.2%, confirming its physical stability.

Example 3

A pharmaceutical aerosol composition was prepared, comprising C2, anhydrous ethanol as co-solvent, PVP (K25) as surfactant, PEG600 as surfactant and HFA227 propellant, as reported in Table 5:

Table 5

COMPONENT	µg/actuation	Quantity
C2	200	0.23%w/w
Anhydrous ethanol	4284	5%w/w
PVP (K25)	85.68	0.1%w/w
PEG600	42.84	0.05%w/w
HFA227	81068	94.62%w/w
Total	85681	100%w/w

Delta T for the formulation reported in table 5, after 10 minutes, is less than 0.2%, confirming its physical stability.

Example 4

A pharmaceutical aerosol composition was prepared, comprising C2, anhydrous ethanol as co-solvent, PVP (K25) as surfactant and HFA134a propellant, as reported in Table 6.

Table 6

Component	µg/actuation	Quantity
C2	200	0.26% w/w
Anhydrous ethanol	3780	5% w/w
PVP (K25)	75.6	0.1% w/w
HFA 134ea	71544	94.64% w/w
Total	75600	100% w/w

Aerosol Characterization with NGI

Table 7

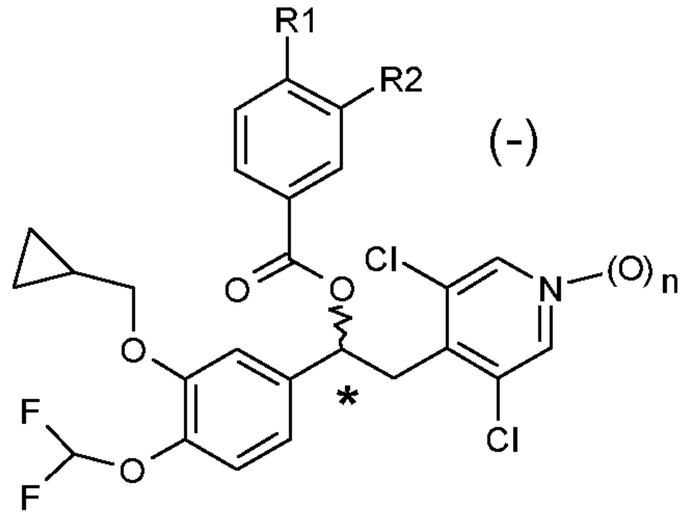
Delivered Dose [µg]	Fine Particle Mass [µg]	Fine Particle Fraction [%]	MMAD [µm]
167	65	39	2.7

*NGI sampling flow rate=30 l/min

Delta T for the formulation reported in Table 6, after 10 minutes, is less than 0.2%, confirming its physical stability.

CLAIMS

1. A pharmaceutical formulation for aerosol administration comprising the (-) enantiomer of a compound of general formula (I)



(I)

wherein:

n is 0 or 1;

R_1 and R_2 may be the same or different, and are selected from the group consisting of:

- linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms;
- OR_3 wherein R_3 is a linear or branched (C_1-C_6)alkyl optionally substituted with one or more halogen atoms or (C_3-C_7)cycloalkyl groups; and
- $HNSO_2R_4$ wherein R_4 is a linear or branched (C_1-C_4)alkyl optionally substituted with one or more halogen atoms,

wherein at least one of R_1 and R_2 is $HNSO_2R_4$

and a propellant.

2. The formulation according to claim 1, which is in the form of suspension.

3. The formulation according to any one of claims 1 to 2, which comprises a surfactant.

4. The formulation according to claim 3, wherein the surfactant is PEG 600 or PVP (K25) or a mixture of them.

5. The pharmaceutical formulation according to any one of claims 1 to 4, which comprises a co-solvent.

6. The pharmaceutical formulation according to claim 5, wherein the co-solvent is ethanol.

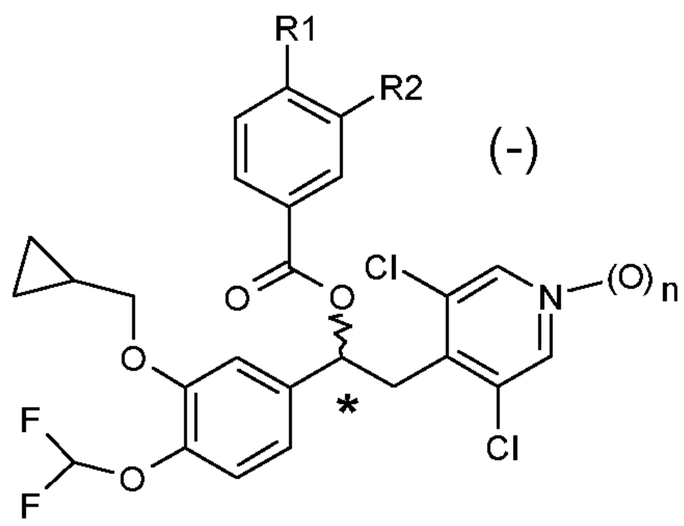
7. The formulation according to any one of claims 1 to 6 wherein the amount of a compound of general formula (I) is comprised between 0.02 w/w and 0.7 w/w.

8. The formulation according to any one of claims 1 to 7 wherein the propellant is a hydrofluoroalkane selected from the group consisting of 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA227) and mixtures thereof.

9. The formulation according to any one of claims 1 to 8 wherein a compound of general formula (I) is administered at a daily therapeutically effective dose comprised between 10 µg and 2000 µg, preferably 20 µg and 1000 µg, more preferably 50 µg and 800 µg, even more preferably 80 µg and 700 µg, even more preferably 300µg and 600 µg.

10. A pressurized metered dose inhaler (pMDI) containing the formulation according to any one of claims 1 to 9.

11. A pharmaceutical formulation for nebulisation comprising a compound of general formula (I)



(I)

wherein:

n is 0 or 1;

R_1 and R_2 may be the same or different, and are selected from the group consisting of:

- linear or branched C_1-C_6 alkyl, optionally substituted with one or more halogen atoms;
- OR_3 wherein R_3 is a linear or branched (C_1-C_6)alkyl optionally substituted with one or more halogen atoms or (C_3-C_7)cycloalkyl groups; and
- $HNSO_2R_4$ wherein R_4 is a linear or branched (C_1-C_4)alkyl optionally substituted with one or more halogen atoms,

wherein at least one of R_1 and R_2 is $HNSO_2R_4$

and a solvent.

12. The pharmaceutical formulation according to claim 11, wherein the solvent is selected from water or an aqueous solution and a water-miscible co-solvent.

13. A single or multidose vial containing the formulation according to claims 11 or 12 to be administered by using suitable nebulizing apparatus.

14. The formulation according to any one of claims 1 to 13, for use as a medicament.

15. The formulation according to any one of claims 1 to 13, for use in the prevention and/or treatment of an inflammatory or obstructive airway disease.