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(54) Titre : FORMULATIONS HFA DE BETA 2-AGONISTES A ACTION PROLONGEE DE DERIVES DE 2(1H)-QIUNOLINONE

(54) Title: PRESSURISED METERED DOSE INHALERS CONTAINING SOLUTIONS OF BETA-2 AGONISTS

(57) Abrégé/Abstract:
The present invention relates to a pharmaceutical formulation for use in the administration of 2(1H)-quinolinone derivatives long-acting β_2-agonists by inhalation. In particular this invention relates to a chemically stable highly efficient TA 2005 HFA solution formulation to be administered by pressurised metered dose inhalers (pMDIs) characterized by a deep lung penetration. The invention also relates to methods for the preparation of said formulation and to its use in respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD).

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PRESSURISED METERED DOSE INHALERS CONTAINING SOLUTIONS OF BETA-2 AGONISTS

Background of the invention

Asthma is a disease which is becoming more prevalent and is the most common disease of childhood. It can be identified by recurrent wheeze and intermittent air flow limitation. Despite many advances in its understanding, said pathology remains a poorly understood and often poorly treated disease. Previously, contraction of airway smooth muscles has been regarded as the most important feature of asthma. Recently there has been a marked change in the way asthma is managed, stemming from the fact that asthma is recognized as a chronic inflammatory disease. Uncontrolled airway inflammation may lead to mucosal damage and structural changes giving irreversible narrowing of the airways and fibrosis of the lung tissue. Therapy should therefore be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating the underlying inflammation.

Another respiratory disease whose incidence is steadily increasing throughout the world is chronic obstructive pulmonary disease (COPD). Most patients with COPD have acquired their lung disease through smoking cigarettes. Depending upon trends in tobacco smoking, it is set to rise to fifth most prevalent cause of disability, worldwide by 2020 (Leckie M et al *Exp Opin Invest Drugs* 2000, 9, 3-23).

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema.

Chronic bronchitis is characterized by excessive secretion of bronchial mucus, whereas emphysema denotes abnormal, permanent enlargement of air spaces distal to the terminal bronchiole, with destruction of their walls and

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without obvious fibrosis (American Toracic Society). Each condition is treated as specific diseases.

Chronic obstructive bronchiolitis is due to obstruction of the peripheral airways as a result of inflammation in the bronchioles.

β_2-Adrenoceptor agonists have been the mainstay of treatment for asthma for many years in view of their prompt bronchodilation effects. Previous researches have also shown that β_2-agonists have potent anti-inflammatory capabilities, e.g. represented by suppression of release of the pro-inflammatory cytokines.

The first generation drugs such as salbutamol or fenoterol were characterized by a relatively short duration of action which has been considered as a disadvantage particularly for patients with nocturnal asthma. Moreover, they have limited effects in COPD, since this disease involves 'irreversible' airways obstruction. The development of longer acting β_2-agonists such as formoterol, salmeterol and TA 2005 has therefore been heralded as a major new development in the treatment of asthma. According to some authors, long-acting β_2-agonists (LABAs) may have acute anti-inflammatory activity in vivo (Johnson M *Clin Exp Allergy 1992, 22, 177-181;* Stelmach I et al *Ann Allergy Asthma Immunol 2002, 89, 67-73*). These drugs are a new interesting therapeutic option for patients with chronic obstructive pulmonary disease (COPD) as well since they have been shown to significantly improve lung function and symptom control.

β_2-adrenergic agonists can also stimulate alveolar fluid clearance in several animal species and in ex vivo rat and human lungs. In view of these findings beta-adrenergic agonist therapy has been proposed as a possible treatment for accelerating the resolution of pulmonary edema in patients with acute pulmonary edema (Sacuma T et al *Am J Respir Crit Care Med 1997, 155, 506-512*). Treatment with β_2-agonists may also increase the secretion of

surfactant and perhaps exert an anti-inflammatory effect, thus helping to restore vascular permeability of the lung (Ware L et al *New Eng. J Med* 2000, 342, 1334-1349.

Drugs intended for the treatment of lung diseases such as asthma and COPD are currently administered by pulmonary delivery which relies on inhalation of an aerosol through the mouth and throat so that the drug substance can reach the lung. They can be administered as aqueous or hydroalcoholic formulations through a nebuliser, as dry powders by means of Dry Powder Inhalers or in halogenated hydrocarbon propellants. The propellant-based systems require suitable pressurized metered-dose inhalers (pMDIs) which release a metered dose of medicine upon each actuation. The relevant formulations can be in the form of solutions or suspensions. Solution formulations, with respect to suspensions, do not present problems of physical stability of the suspended particles and so could guarantee a higher dose uniformity and reproducibility. As far as the type of propellant is concerned, hydrofluoroalkanes [(HFAs) known also as hydro-fluoro-carbons (HFCs)] would be mandatory propellants as chlorofluorocarbons (known also as Freons or CFCs), which were for many years the preferred propellants aerosols for pharmaceutical use, have been implicated in the destruction of the ozone layer so their use is being phased out. In particular, 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) have been acknowledged to be the best candidates for non-CFC propellants and a number of pharmaceutical aerosol formulations using such HFA propellant systems have been disclosed.

In developing a therapeutic aerosol, the aerodynamic size distribution of the inhaled particles is the most important variable in defining the site of droplet or particle deposition in the lungs of the patient; in short, it will determine whether drug targeting succeeds or fails. See P. Byron, "Aerosol

Formulation, Generation, and Delivery Using Nonmetered Systems, "Respiratory Drug Delivery, 144-151,144 (CRC Press, 1989).

Thus, a prerequisite in developing a therapeutic aerosol is a preferential particle size.

When the formulation is in the form of suspension, the particle size of the cloud is dominated by the particle size of the suspended drug, defined by the milling/micronization process. When the formulation is in the form of solution, the volumetric contribution of suspended drug particles is absent and much finer liquid droplets clouds, largely defined by the drug concentration in the solution, are generated.

Solid particles and/or droplets in an aerosol formulation can be characterized by their mass median aerodynamic diameter (MMAD, the diameter around which the mass aerodynamic diameters are distributed equally).

Particle deposition in the lung depends largely upon three physical mechanisms:

i) impaction, a function of particle inertia;

ii) sedimentation due to gravity; and

iii) diffusion resulting from Brownian motion of fine, submicrometer (< 1 microns) particles.

The mass of the particles determines which of the three main mechanisms predominates.

For aerosol therapy of drugs which topically act on the smooth muscle of the conducting airways, and in particular for β_2-agonists, it has been reported in the past that particles should preferentially deposit in the upper-to mid-pulmonary region (bronchiole region), so they should have a MMAD of about 1.5(2.0) to about 5.0 microns, preferably approximately 3 microns (Zanen P et al *Int J Pharm* 1994, 107, 211-217; *Int J Pharm* 1995, 114, 111-

115; *Thorax*, 1996, 51, 977-980).

In fact, particles having aerodynamic diameters of greater than about 5 microns generally do not reach the lung since they tend to impact the back of the throat and are swallowed and possibly orally absorbed, while particles smaller than 1.5 (2.0) micron, i. e., about 0.5 to about 2 microns, capable of reaching the alveolar region, have been considered undesirable because they can be absorbed into the bloodstream and might enhance the undesired systemic effects of the drugs. Particles having diameters smaller than about 0.5 microns have been generally considered as not therapeutically useful as they can be exhaled.

Accordingly, pMDI formulations of β_2-agonist have traditionally been formulations able to deliver particles whose larger fraction is comprised between 2 and 5 microns and the amount of those below 1 micron is very limited since the former are small enough to reach the upper-to mid-pulmonary region, but are too large to reach the alveoli. This is also the inherent particle size of the formulation in the form of suspensions as conventional micronization (air-jet milling) of pure drug substance can reduce the drug particle size to about 2-3 microns.

On the other hand, it is known that the density of the beta-adrenergic receptors is higher in the distal tract of the bronchioles (Barnes P et al *Am Rev Respir Dis* 1983, 127, 758-762), a region which is better reached by smaller particles. Moreover inflammation in asthma in not merely confined to the large central airways but also extends to small peripheral airways. The eosinophilic inflammation process which has been seen to be associated to asthma concerns both the bronchial and the alveolar districts (Wang S *J Immunol* 2001, 166, 2741-2749). Recently, Martin R in *J Allergy Clin Immunol* 2002, 109 (Suppl 2), 447-460 reported that distal lung diseases appear to increase the risk of recurrent asthma exacerbation, while disease-

related anatomic changes in the small airways of the distal lung are prominent in fatal asthma. In this respect, in his opinion, the administration of drug with particles of a diameter of about 1 micron (referred as "extrafine" aerosols) could be advantageous. The clinical significance of distal lung disease makes this region an important therapeutic target so particles able to reach and deposit into such region could better contribute to the management of the disease. It has been also reported that, among the particles smaller than 0.5 micron, those with a diameter less or equal than 0.3 micron, preferably between 5 and 300 nm, can be deposited in the alveolar region of the lung by sedimentation. This range of particle has been referred to in the literature as "ultrafine" particles.

"Ultrafine" particles generated from di-2-ethylhexyl sebacate (DEHS) as a model, have also been reported to have a good airway penetration (Anderson P et al *Chest* 1990, 97, 1115-1120). Amirav I et al in *J Nucl Med 2002, 43, 487-491* emphasize the need for improvement in aerosol delivery by targeting narrow peripheral airways with superfine aerosols in the treatment of inflammation airways diseases and in particular in acute bronchiolitis.

Therefore medicinal aerosol particles having a diameter < 0.1 μm can be particularly effective in case of airway obstruction in asthmatic subjects wherein the pathology is associated with mucus hypersecretion which hinders the diffusion of the drug or in patients affected by obstructive lung diseases such as COPD. Intuitively indeed, one would expect the reduction in the lumen of airways by mucus and permanent constriction would require finer clouds for perfusion.

Nevertheless, sub-micron aerosol formulations (including HFA formulations) have only been reported until now as microemulsions containing surface active agents such as lecithin (WO 01/78689, WO 00/27363; Dickinson P et al *J Drug Target* 2001, 9, 295-302).

In virtue of the inherent anti-inflammatory properties of LABAs, relevant formulations capable of delivering a significant fraction of fine particles would be expected to be of great advantage in patients affected by broncho-pulmonary obstructive diseases.

2(1H)-quinolinone derivatives β_2-agonist have been described as potent and long-acting compounds (EP 147 719; WO 00/75114).

In particular, 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino] ethyl] -2(1H)-quinolinone has been reported as a highly potent β_2-agonist, also characterized by a rapid onset of action, which by virtue of its peculiar long duration of action can be administered once a day. Its hydrochloride salt is known under the experimental code TA 2005.

HFA solution formulations of β_2-agonists for aerosol delivery through pressurized metered-dose inhalers are known.

WO 94/13262, in the name of Boehringer Ingelheim, provides aerosol solution formulations comprising a medicament, an HFC propellant, a cosolvent and an inorganic or an organic acid as a stabiliser for preventing the chemical degradation of the active ingredient. Most examples relate to ipratropium bromide, an anticholinergic drug. As far as β_2-agonists are concerned, only formulations containing fenoterol, a short acting derivative not chemically related to the compounds of the invention are exemplified. Furthermore, apart from ipratropium bromide, WO 94/13262 gives no guidance with respect to the amount of acid which has to be added in order to stabilise the medicaments without compromising the stability of the whole composition in the can. The only hint can be found on page 5, lines 15 to 16 which says that an amount of inorganic acid should be added to obtain a pH value from 1 to 7, so a very broad and generic range. As far as the water content is concerned, in the application it is stated that a small amount of

water (up to about 5% by weight) may also be present in the propellant/cosolvent system. In the case of ipratropium bromide, it is reported that addition of 1% water reduces the decomposition due to dehydration.

WO 98/34596, in the name of 3 M, refers to solution formulations containing a propellant and a physiologically acceptable polymer which could help the solubilisation and the stability as well of the active ingredients.

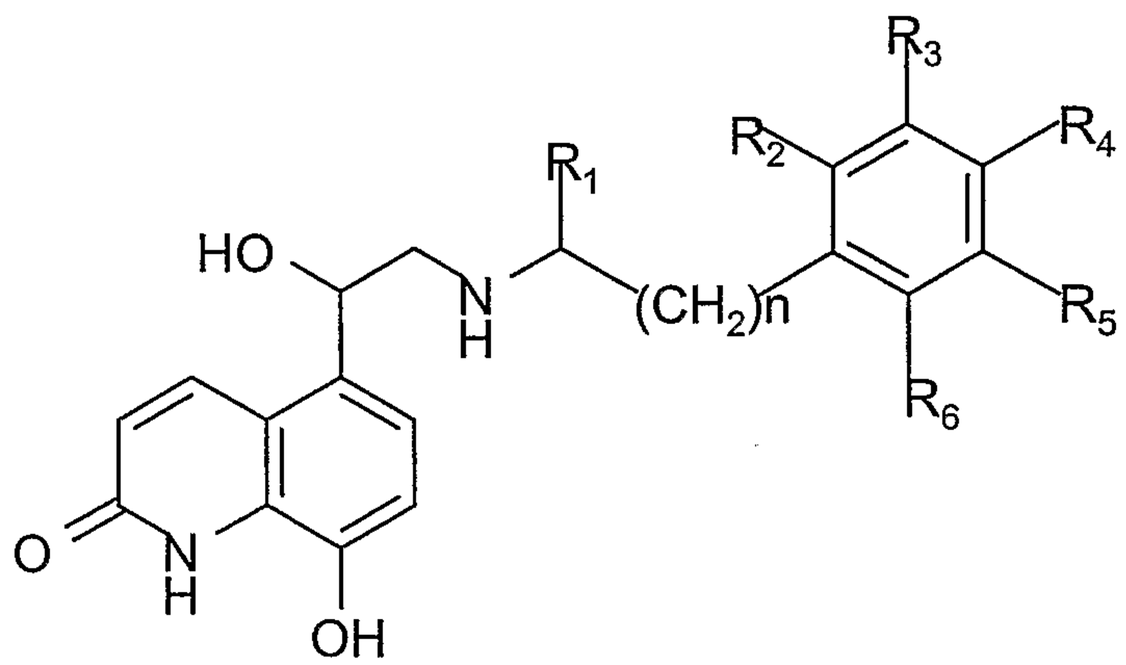
In WO 98/56349 the applicant described solution compositions for use in an aerosol inhaler, comprising an active material, a propellant containing a hydrofluoroalkane (HFA), a co-solvent and further comprising a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. In some cases a small quantity of water may be added to the composition to improve the solution of the active material and/or the low volatility component in the cosolvent.

In EP 1157689 the applicant disclosed aerosol pharmaceutical compositions comprising a β_2-agonist belonging to the class of phenylalkylamino derivatives in solution in a HFA propellant, a co-solvent whose apparent pH has been adjusted to between 2.5 and 5.0 in order to guarantee an adequate shelf-life. In a particular embodiment of the invention, isopropyl myristate (IPM) as a low-volatility is added in order to either increase the MMAD of the aerosol particles and further improving the stability of the formulation. As far as the role of water is concerned, it is only reported that humidity, in the case of certain active ingredients could be detrimental to the chemical stability during storage. In EP 1 157 689 it is generically stated that TA 2005 formulations will be advantageously suitable for delivering 2-10 μg/dose, preferably 3-5 μg/dose. A 3.5 μg/dose HFA 134a formulation containing 12% w/w ethanol and 1.0% IPM in order to increase the MMAD of the delivered particles and to improve the stability of the formulation is reported in example 7.

In view of the above considerations, it would be highly advantageous to provide highly efficient 2(1H)-quinolinone derivatives long acting β_2-agonist formulations to be administered by pMDI characterized by a deeper lung penetration and a low systemic exposure.

Description of the invention

The object of the present invention is to provide a pharmaceutical aerosol solution formulation to be administered by pMDI, having a suitable shelf-life for pharmaceutical use, comprising an active ingredient selected from 2(1H)-quinolinone derivatives long acting β_2-agonists of formula (I)



(I)

where R_1 is methyl and R_2 is hydrogen or R_1 and R_2 form a methylenic bridge $(CH_2)_n$

n is 1 or 2

R_3, R_4, R_5 and R_6 are each independently hydrogen, hydroxy, C_1-C_4 straight chain or branched alkyl, C_1-C_4 straight chain or branched alkyl substituted by one or more halogen and/or hydroxy, halogen, C_1-C_4 straight chain or branched alkoxy, enantiomers, salts and solvates thereof;

a HFA propellant and a suitable amount of co-solvent wherein the active ingredient is completely dissolved in the propellant-cosolvent system.

Said solution provides on actuation of the formulation a fraction of particles equal or less than 1.1 micron of at least 30% as defined by the

content stages S6-AF of an Andersen Cascade Impactor relative to the total amount of the fine particle dose collected in the stages S3-AF of the impactor.

The formulation of the invention is able to deliver a significant fraction of particles having a diameter equal or less than 1.1 micron, comprising both extrafine particles, according to the definition of Martin R in *J Allergy Clin Immunol 2002, 109 (Suppl 2), 447-460* and particles having a diameter equal or less than 0.3 micron (ultrafine particles, according to the definition of other authors). By virtue of these characteristics the formulation of the invention will be hereinafter referred to as superfine formulation.

As a particular aspect of the present invention, we provide a pharmaceutical aerosol formulation comprising 0.005-0.016% w/v 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino] ethyl] -2(1H)-quinolinone or one of its pharmaceutically acceptable salt or solvates as active ingredient in solution in a liquefied HFA propellant and a co-solvent preferably selected from a pharmaceutically acceptable alcohol, characterized in that the fraction of particles equal or less than 1.1 micron is higher than or equal to 30% as defined by the content of stages S6-AF of an Andersen Cascade Impactor relative to the total amount of the fine particle dose collected in the stages S3-AF of the impactor. The preferred active ingredient is 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino] ethyl] -2(1H)-quinolinone hydrochloride from now onwards defined as TA 2005. In certain formulations a proper amount of water up to 5% w/w of the total weight of the formulation can be added. Advantageously the pH of the formulation is to between 2.5 and 5.0 as determined in the model vehicle system reported in EP 1157689.

The formulations of the invention can also comprise a further active ingredient. In particular, the addition of a corticosteroid to a long-acting β_2-agonist gives optimal control of asthma in most patients and relevant fixed

combinations are increasingly used as a convenient controller in patients with persistent asthma. It has also been reported that each class of drug enhances the beneficial actions of the other. In fact, corticosteroids increase the expression of β_2-receptors and protect them against down-regulation in response to long-acting β_2-agonist exposure, whereas β_2-agonist may enhance the anti-inflammatory actions of corticosteroids (Barnes P et al. *Eur Respir J* 2002, 19, 182-191).

Accordingly, another object of the present invention is to provide highly efficient formulations containing a 2(1H)-quinolinone derivative β_2 agonist as active ingredient, further comprising a steroid. The high fraction of superfine particles of the formulation of the invention can allow both drugs to reach the small peripheral airways region in such a way as to better exercise their synergic effects in distal lung diseases. Moreover, in view of the aforementioned characteristics, it might be possible to develop formulations comprising fixed combinations of the β_2 agonist and a steroid wherein the latter one could be present in a lower dose, by maintaining the same therapeutic effect.

A further aspect of the present invention is to provide highly efficient 2(1H)-quinolinone derivatives long-acting β_2-agonist formulations in combination with an anticholinergic atropine-like derivative such as ipratropium bromide, oxitropium bromide and tiotropium bromide in order to provide a medicament particularly effective for the treatment of COPD.

It is also provided a method of filling an aerosol inhaler with a composition of the invention, the method comprising:

(a) preparation of a solution of one or more active ingredients in one or more co-solvents;

(b) optionally adding a pre-determined amount of water and/or adjusting the pH of the solution;

(c) filling of the device with said solution;

(d) crimping with valves and gassing;

(e) adding a propellant containing a hydrofluoroalkane (HFA).

A still further aspect of the invention comprises the use of the β_2 agonist fully dissolved in the propellant / co-solvent system and capable of providing on actuation a fraction of at least 30% of emitted particles with an aerodynamic diameter equal or less than 1.1 microns, for the preparation of a medicament for the treatment of respiratory disorders such as asthma and COPD.

In view of its technical feature of providing on actuation a fraction of particles with an aerodynamic diameter of less than 1.1 micron, of at least 30%, the formulation of the invention can be particularly effective for the treatment of asthma, COPD and, generally, of airway obstruction conditions wherein the pathology is associated with mucus hypersecretion which hinders the diffusion of the drug.

Furthermore, it may be clinically useful as a treatment to hasten the resolution of alveolar edema and of surfactant-deficiency related diseases such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Detailed description of the invention

The aerosol formulations of the invention comprise a 2(1H)-quinolinone derivative long acting β_2-agonist of formula (I) as active ingredient, an HFA propellant and a co-solvent wherein the active ingredient is fully dissolved in such a way that the formulations are able of providing on actuation a fraction of emitted particles of equal or less than 1.1 microns higher or equal to 30% as defined by the content stages S6-AF of an Andersen Cascade Impactor relative to the total fine particle dose collected in the stages S3-AF of the impactor, advantageously higher than 40%, preferably higher than 50%, more preferably higher than 60%, even more preferably higher than 70%. Advantageously, the

formulations of the invention are free of other excipients such as surfactants besides the solubilisation agent, the propellant and, optionally, water.

The formulations may contain up to 5% w/v of the active ingredient, for example 0.0001% to 5%, 0.0005% to 3%, 0.001% to 1%, 0.001 to 0.005% w/v.

Examples of HFA propellants include 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA227) and mixtures thereof. The preferred propellant is 1,1,1,2-tetrafluoroethane (HFA134a). An alternative propellant of interest is 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA227).

The co-solvent is selected from the group of lower alkyl (C_1-C_4) alcohols, polyols, polyalkylene glycols and their combinations. Other suitable co-solvents are (poly)alkoxy derivatives including polyalkoxy alcohols, [such as 2-(2-ethoxyethoxy) ethanol available under the trademark Transcutol®].

Preferably the co-solvent is an alcohol. The preferred one is ethanol.

The concentration of the co-solvent (e.g. ethanol) will vary depending on the final concentration of the active ingredients in the formulation and on the propellant. The amount of ethanol should not exceed around 40% w/w of the total weight of the formulation. Advantageously it is comprised between 5 and 30% w/w, preferably between 10 and 20% w/w, even more preferably between 12 and 15% w/w.

Active ingredients which may be used in the aerosol compositions of the invention are 2(1H)-quinolinone derivatives long acting β_2 adrenergic agonists of formula (I), stereoisomers, physiologically acceptable salts and solvates thereof.

The preferred active ingredient is 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone, in the form of hydrochloride salt (TA 2005).

Said active ingredients can be used alone or in combination with

steroids such as beclometasone dipropionate (BDP), flunisolide, mometasone furoate, fluticasone propionate, ciclesonide, budesonide and its 22R-epimer, with anticholinergic atropine-like derivatives such as ipratropium bromide, oxitropium bromide, tiotropium bromide or with drugs useful for the management of respiratory diseases such as methylxanthines, anti-leukotrienes and phosphodiesterase inhibitors.

The concentration of the active ingredient in the HFA formulation will depend on the therapeutic amount to be delivered preferably in one or two actuations.

In the foregoing formulations are provided for TA 2005 and drug concentrations are given as w/v. The corresponding percentages as (w/w) can be calculated by determining the density of the vehicle.

The formulations will be filled in a canister fitted with a suitable metering valve. We prefer that the formulation is actuated by a metering valve capable of delivering a volume of between 25 µl and 100 µl, e.g. 50 µl or 63 µl. 100 µl is also suitable.

TA 2005 concentration will vary between 0.0005% and 0.024% w/v in order to deliver 0.5-6 µg per actuation, preferably between 0.001% and 0.016% w/v, in order to deliver 1 - 4 µg per actuation, more preferably between 0.001% and 0.008% w/v in order to deliver 1 or 2 µg per actuation. If needed, a drug overage can be done. For instance, for 1 and 2 µg/dose, wherein a 63 µl metering volume is used, the final concentrations of TA 2005 hydrochloride delivered per actuation would be 0.0016% and 0.0032% w/v, respectively.

The intended dose regimen for TA 2005 is twice or once daily, preferably once daily where the suitable daily dose may range up to 8 µg and advantageously ranges from 0.5 to 6 µg, preferably from 1 to 6 µg, more preferably from 2 to 4 µg.

The apparent pH range is advantageously between 2.5 and 5.0,

preferably between 2.8 and 4.0. Strong mineral acids preferably selected from the group of hydrochloric, nitric, phosphoric acid are used to adjust the apparent pH, more preferably hydrochloric acid.

The amount of acid to be added to reach the desired apparent pH will be pre-determined in the model vehicle reported in EP 1157689 and it will depend on the type and concentration of the active ingredient and the amount of the co-solvent.

For 0.001-0.008% w/v TA 2005 in HFA 134a and 15% w/w ethanol, a concentration between 0.01% and 0.05%, preferably between 0.01% and 0.03% on the total weight of the formulation of 0.1 M hydrochloric acid is preferably added.

The presence of water can be especially advantageous when the formulation further contains another active ingredient such as a steroid.

In these cases an amount of water up to 5.0% w/w on the total weight of the formulation might be present, preferably from 0.05% to 3% w/w, even more preferably from 1% to 2% w/w.

The formulations of the invention will be filled into canisters suitable for delivering pharmaceutical aerosol formulations such as plastic or plastic coated glass bottle or preferably a metal can, for example an aluminium can. The formulations can also be filled in canisters having part of all of the internal surfaces made of anodised aluminium, stainless steel or lined with an inert organic coating. Examples of preferred coatings are epoxy-phenol resins, perfluorinated polymers such as perfluoroalkoxyalkane, perfluoroalkoxyalkylene, perfluoroalkylenes such as poly-tetrafluoroethylene (Teflon), fluorinated-ethylene-propylene, polyether sulfone and a copolymer fluorinated-ethylene-propylene polyether sulfone. Other suitable coatings could be polyamide, polyimide, polyamideimide, polyphenylene sulfide or their combinations.

Canisters having the internal surface lined with Teflon might be

preferred for the TA 2005 formulations.

To further improve the stability, cans having a rim with rounded edges, preferably a rolled neck or rolled-in rim, a part or full rollover rim can be used according to the teaching of WO 02/72448.

The canister is closed with a metering valve. The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate 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 and TPE rubbers are preferred. EPDM rubbers are particularly preferred. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (eg. DF10, DF30, DF60), Bespak plc, UK (eg. BK300, BK356, BK357) and 3M-Neotechnic Ltd, UK (eg. Spraymiser). The DF31 valve of Valois, France is also suitable. Valve seals, especially the gasket seal, and also the seals around the metering chamber, will 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.

Valve materials, especially the material of manufacture of the metering chamber, will preferably be manufactured of a material which is inert to and resists distortion by contents of the formulation, especially when the contents include ethanol. Particularly suitable materials for use in manufacture of the metering chamber include polyesters e.g. polybutyleneterephthalate (PBT) and acetals, especially PBT.

Materials of manufacture of the metering chamber and/or the valve stem may be fluorinated, partially fluorinated or impregnated with fluorine containing substances in order to resist drug deposition.

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large-scale batches for the commercial production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminum can to form an empty canister. The medicament is added to a charge vessel and a mixture of ethanol, optionally water and liquefied propellant is pressure filled through the charge vessel into a manufacturing vessel. An aliquot of the formulation is then filled through the metering valve into the canister.

In an alternative process, an aliquot of the liquefied formulation is added to an open canister under conditions which are sufficiently cold that the formulation does not vaporize, and then a metering valve crimped onto the canister.

In an alternative process, an aliquot of medicament dissolved in the solubilising agent is dispensed into an empty canister, a metering valve is crimped on, and then the propellant is filled into the canister through the valve. The processes can be carried out an in inert atmosphere, for instance by insufflating nitrogen, in order to avoid the uptake of humidity from the air.

Each filled canister is conveniently fitted into a suitable channeling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs of a patient. Suitable channeling devices comprise, for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the mouth of a patient e.g. a mouthpiece actuator.

In a typical arrangement the valve stem is seated in a nozzle block which has an orifice leading to an expansion chamber. The expansion chamber has an exit orifice which extends into the mouthpiece. Actuator (exit) orifice diameters in the range 0.15 - 0.45 mm especially 0.2 - 0.45 mm are generally suitable e.g. 0.25, 0.30, 0.33 or 0.42 mm. 0.22 mm is also suitable. For certain

formulations it would be useful to utilize laser-drilled actuator orifices having a diameter ranging from 0.10 to 0.22 mm, in particular from 0.12 to 0.18 mm as those described in the co-pending application n. EP 1130521.6.

The use of such fine orifices also increases the duration of cloud generation and lowers its velocity. These changes facilitate the coordination of cloud generation with the slow inspiration of the patient.

The aerodynamic particle size distribution of each tested formulation of the invention can be characterized using a Multistage Cascade Impactor according to the procedure described in European Pharmacopoeia 2nd edition, 1995, part V.5.9.1, pages 15-17. In this specific case, an Andersen Cascade Impactor (ACI) was utilized operating at a flow rate of 28.3 l/min. Deposition of the drug on each ACI plate was determined by high pressure liquid chromatography (HPLC). Mean delivered dose was calculated from the cumulative deposition in the ACI. Mean respirable dose (fine particle dose) was obtained from the deposition on Stages 3 (S3) to filter (AF) corresponding to particles $\leq$ 4.7 microns, divided by the number of actuation per experiment, while mean "superfine" dose was obtained from the deposition on Stages 6 to filter corresponding to particles $\leq$ 1.1 microns.

Administration of the formulations of the invention may be indicated for the 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 can also benefit of this kind of formulation.

The invention is illustrated with reference to the following examples.

Example 1 Superfine TA 2005 HFA formulations

A formulation for delivering a nominal dose of 1 μg per actuation of

active ingredient was prepared with the composition as follows:

Components	*Amounts*		
	Per unit		Nominal dose
	mg	%	µg
TA 2005	0.15	0.0016 w/v	1
Ethanol	1650	15 w/w	-
HCl 0.1 M	2.0 *	0.018 w/w	-
HFA 134a q.s. to 9.45 ml	9347.85	-	-

* equivalent to 2.0 µl

The formulation (120 actuations/canister, overage of 30 actuations) was filled in aluminum canisters having the internal surface coated with Teflon (two stage pressure filling) and fitted with a metering valve having a 63 µl metering chamber. An actuator with an orifice diameter of 0.22 mm was used. Results were obtained as a mean of 2 cans.

Analogously, formulations able of delivering a nominal dose of 2, 3 or 4 µg per actuation of active ingredient can be prepared. The aerodynamic particle size distribution was measured by ACI, according to page 16 lines 10 to 18 and the delivery characteristics of each formulation were determined in terms of the following parameters i) nominal dose: theoretical dose per single actuation; ii) delivered dose: amount of active particles deposited into the all ACI stages; iii) respirable dose (fine particle dose): amount of active particles of size less than 4.7 microns (S3-AF); iv) respirable fraction (fine particle fraction): ratio between the respirable dose and the delivered dose; v) "superfine" dose: amount of active particles equal or less than 1.1 microns (S6-AF); iv) "superfine" fraction: ratio between the "superfine" dose and the respirable dose.

The formulation of the invention gives rise upon actuation to a very

high percentage of particles with a diameter less than 1.1 microns. For certain formulations depending on the percentage of active ingredient and amount of co-solvent, superfine fractions of more than 80% can be achieved.

Despite the presence of such a high fraction of particles having a diameter equal or less than 1.1 micron in the formulation, at the therapeutic doses the drug has been well tolerated.

A stability study on a formulation able to deliver 4 μg per actuation was initiated storing the cans upright at 5°C.

After nine months the TA 2005 assay is higher than 95% and therefore meets the requirements of the ICH guideline Q1A referring to "Stability Testing of new Active Substances (and Medicinal Products)".

Example 2 Superfine HFA formulation comprising TA 2005 and 22R-budesonide

A formulation for delivering, respectively, a nominal dose of 1 μg of TA 2005 and 80 μg of 22R-budesonide per actuation was prepared with the composition as follows:

Components	*Amounts*		
	Per unit		Nominal dose
	mg	%	μg
TA 2005	0.15	0.0016 w/v	1
22R-budesonide	12.00	0.127 w/v	80
Ethanol	1650	15 w/w	-
HCl 0.1 M	3.3*	0.03 w/w	-
Water	220.05	2.0 w/w	
HFA 134a q.s. to 9.45 ml	9114.5	-	-

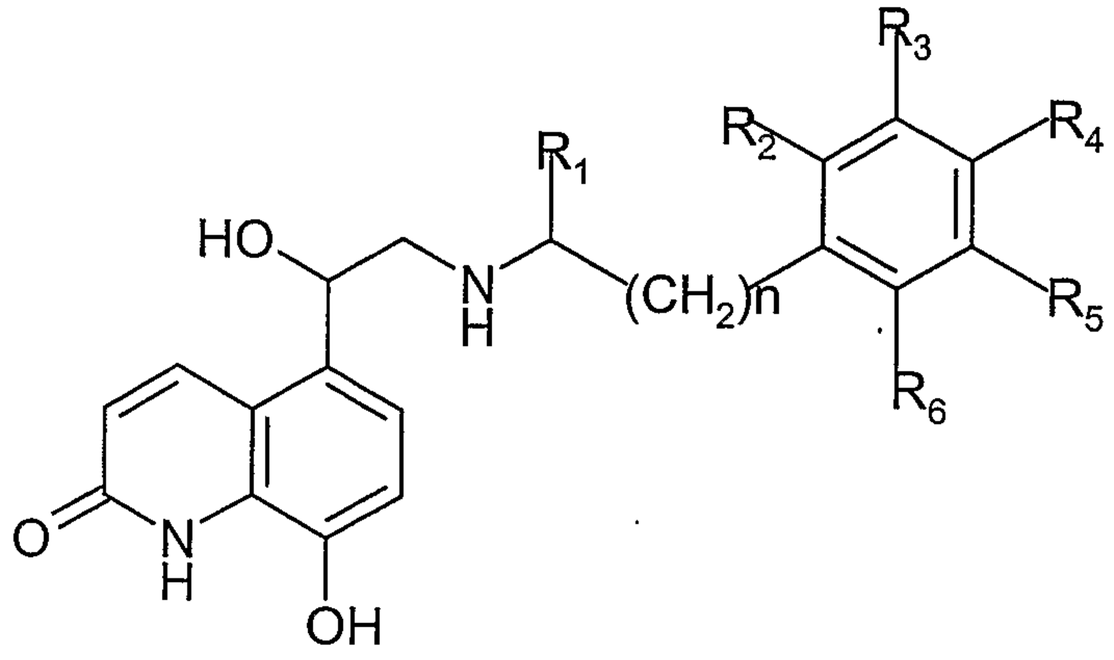
* equivalent to 3.3 μl

The formulation (120 actuations/canister, overage of 30 actuations) was filled in aluminum canisters having the internal surface coated with Teflon (two stage pressure filling) and fitted with a metering valve having a 63 µl metering chamber.

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CLAIMS

1. A pharmaceutical aerosol formulation to be administered by pressurized metered dose inhalers which comprises an active ingredient selected from a 2(1H)-quinolinone derivative long acting β_2- agonist of formula:



(I)

where R_1 is methyl and R_2 is hydrogen or R_1 and R_2 form a methylene bridge $(CH_2)_n$

n is 1 or 2

R_3, R_4, R_5 and R_6 are each independently hydrogen, hydroxy, C_1-C_4 straight chain or branched alkyl, C_1-C_4 straight chain or branched alkyl substituted by one or more halogen and/or hydroxy, halogen, C_1-C_4 straight chain or branched alkoxy, a stereoisomer, physiologically acceptable salt and solvate thereof, in a solution of a liquefied HFA propellant, a co-solvent, and optionally an amount of water up to 5% on the total weight of the formulation.

2. A pharmaceutical formulation according to claim 1 wherein the fraction of particles equal or less than 1.1 μm delivered on actuation of the inhaler is higher or equal than 30% as defined by the content of the stages S6-AF of an Andersen Cascade Impactor, relatively to the content of the stages S3-AF, according to the method referred to in the description on page 16 lines 10 to 18.

3. A pharmaceutical formulation according to claims 1-2 wherein the superfine fraction is higher than 50%.

4. A pharmaceutical formulation according to claims 1-3 wherein the active ingredient is 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxy-phenyl)-1-methylethyl]amino] ethyl] -2(1H)-quinolinone, a physiologically acceptable salt or a solvate thereof.

5. A pharmaceutical formulation according to claims 1-3 wherein the active ingredient is 8-hydroxy-5-[(1R)-1-hydroxy-2-[[(1R)-2-(4-methoxy-phenyl)-1-methylethyl]amino] ethyl] -2(1H)-quinolinone hydrochloride.

6. A pharmaceutical formulation according to claim 5 wherein the active ingredient is in a concentration comprised between 0.0005 and 0.024% w/v.

7. A pharmaceutical formulation according to claim 5 wherein the active ingredient is in a concentration comprised between 0.001 and 0.008% w/v.

8. A pharmaceutical formulation according to any preceding claim wherein the pH is comprised between 2.5 and 5.0.

9. A pharmaceutical formulation according to any preceding claim wherein the pH is comprised between 2.8 and 4.0.

10. A pharmaceutical formulation according to claims 8 and 9 wherein the pH is adjusted by adding hydrochloric acid.

11. A pharmaceutical formulation according to any preceding claim, wherein the propellant includes one or more hydrofluoroalkanes [HFAs] selected from the group comprising HFA 134a and HFA 227.

12. A pharmaceutical formulation according to any preceding claim, wherein the co-solvent is selected from the group of lower alkyl (C_1-C_4) alcohols, polyols, polyalkylene glycols, (poly)alkoxy derivatives and their combinations.

13. A pharmaceutical formulation according to claim 12 wherein the co-solvent is ethanol.

14. A pharmaceutical formulation according to claim 6 further comprising 15% w/w ethanol, from 0.01% to 0.05% w/w HCl 0.1 M and HFA 134 a.

15. A pharmaceutical formulation according to any preceding claim filled in a canister having part or all of its internal metallic surfaces lined with an inert organic coating.

16. A pharmaceutical formulation according to claim 15, wherein the canister is lined with an inert organic coating selected from epoxy-phenol resins, perfluoroalkoxyalkane, perfluoroalkoxyalkylene, perfluoroalkylenes such as polytetrafluoroethylene, fluorinated-ethylene-propylene, polyether sulfone and a copolymer fluorinated-ethylene-propylene polyether sulfone.

17. A pharmaceutical formulation according to claim 16 wherein the inert organic coating is polytetrafluoroethylene (Teflon).

18. A pharmaceutical formulation according to any preceding claim further comprising a further active ingredient selected from the class of steroids such as beclomethasone dipropionate, fluticasone propionate, ciclesonide, budesonide and its 22R-epimer or anticholinergic atropine-like derivatives such as ipratropium bromide, oxitropium bromide and tiotropium bromide.

19. A method of preparing the formulations of claims 1-18, the method comprising:

(a) preparing of a solution of one or more active ingredients in one or more co-solvents;

(b) optionally adding a pre-determined amount of water and/or adjusting the pH of the solution;

(c) filling of the device with said solution;

(d) crimping with valves and gassing;

(e) adding a propellant containing a hydrofluoroalkane (HFA).