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(57) Abstract

This invention relates to aerosol formulations of use for the administration of medicaments by inhalation, in particular a pharmaceutical aerosol formulation which comprises particulate medicament selected from the group comprising salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical aerosol formulation as defined is also described.

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MEDICAMENTS

This invention relates to aerosol formulations of use for the administration of medicaments by inhalation.

The use of aerosols to administer medicaments has been known for several decades. Such aerosols generally comprise the medicament, one or more chlorofluorocarbon propellants and either a surfactant or a solvent, such as ethanol. The most commonly used aerosol propellants for medicaments have been propellant 11 (CCl_3F) and/or propellant 114 (CF_2ClCF_2Cl) with propellant 12 (CCl_2F_2). However these propellants are now believed to provoke the degradation of stratospheric ozone and there is thus a need to provide aerosol formulations for medicaments which employ so called "ozone-friendly" propellants.

A class of propellants which are believed to have minimal ozone-depleting effects in comparison to conventional chlorofluorocarbons comprise fluorocarbons and hydrogen-containing chlorofluorocarbons, and a number of medicinal aerosol formulations using such propellant systems are disclosed in, for example, EP 0372777, WO91/04011, WO91/11173, WO91/11495 and WO91/14422. These applications are all concerned with the preparation of pressurised aerosols for the administration of medicaments and seek to overcome the problems associated with the use of the new class of propellants, in particular the problems of stability associated with the pharmaceutical formulations prepared. The applications all propose the addition of one or more of adjuvants such as alcohols, alkanes, dimethyl ether, surfactants (including fluorinated and non-fluorinated surfactants, carboxylic acids, polyethoxylates etc) and even conventional chlorofluorocarbon propellants in small amounts intended to minimise potential ozone damage.

Thus, for example EP 0372777 requires the use of 1,1,1,2-tetrafluoroethane in combination with both a cosolvent having greater polarity than 1,1,1,2-tetrafluoroethane (e.g. an alcohol or a lower alkane) and a surfactant in order to achieve a stable formulation of a medicament powder. In particular it is noted in the specification at page

3, line 7 that "it has been found that the use of propellant 134a (1,1,1,2-tetrafluoroethane) and drug as a binary mixture or in combination with a conventional surfactant such as sorbitan trioleate does not provide formulations having suitable properties for use with pressurised inhalers". Surfactants are generally recognised by those skilled in the art to be essential components of aerosol formulations, required not only to reduce aggregation of the medicament but also to lubricate the valve employed, thereby ensuring consistent reproducibility of valve actuation and accuracy of dose dispensed. Whilst WO91/11173, WO91/11495 and WO91/14422 are concerned with formulations comprising an admixture of drug and surfactant, WO91/04011 discloses medicinal aerosol formulations in which the particulate medicaments are pre-coated with surfactant prior to dispersal in 1,1,1,2-tetrafluoroethane.

We have now surprisingly found that, in contradistinction to these teachings, it is in fact possible to obtain satisfactory dispersions of certain medicaments in fluorocarbon or hydrogen-containing chlorofluorocarbon propellants such as 1,1,1,2-tetrafluoroethane without recourse to the use of any surfactant or cosolvent in the composition, or the necessity to pre-treat the medicament prior to dispersal in the propellant. More particularly, satisfactory dispersions may be formed where the medicament is selected from salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof.

There is thus provided in one aspect of the invention a pharmaceutical aerosol formulation which comprises particulate medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates (for example hydrates) thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant. By "substantially free of surfactant" is meant formulations which contain no significant amounts of surfactant, for example less than 0.0001% by weight of the medicament.

In an alternative embodiment the present invention provides a pharmaceutical aerosol formulation as hereinbefore defined with the proviso that when said formulation consists

essentially of salbutamol and 1,1,1,2-tetrafluoroethane in a weight ratio of 0.05:18, said salbutamol is present in the form of a physiologically acceptable salt.

The particle size of the particulate (e.g. micronised) medicament should be such as to permit inhalation of substantially all of the medicament into the lungs upon administration of the aerosol formulation and will thus be less than 100 microns, desirably less than 20 microns, and preferably in the range 1-10 microns, e.g. 1-5 microns.

Suitable pharmaceutically acceptable salts of the medicaments of use in the formulations of the present invention include acid addition salts such as for example sulphates, hydrochlorides and xinafoates (1-hydroxy-2-naphthoate), amine salts or alkali metal salts (e.g. sodium). Salmeterol will preferably be in the form of its xinafoate salt and salbutamol will preferably be in the form of its sulphate salt.

The final aerosol formulation desirably contains 0.005-10% w/w, preferably 0.005 - 5% w/w, especially 0.01-1.0% w/w, of medicament relative to the total weight of the formulation.

The propellants for use in the invention may be any fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof having a sufficient vapour pressure to render them effective as propellants. Preferably the propellant will be a non-solvent for the medicament. Suitable propellants include, for example, C_{1-4}hydrogen-containing chlorofluorocarbons such as CH_2ClF, $CClF_2CHClF$, CF_3CHClF, CHF_2CClF_2, $CHClFCHF_2$, CF_3CH_2Cl and $CClF_2CH_3$; C_{1-4}hydrogen-containing fluorocarbons such as CHF_2CHF_2, CF_3CH_2F, CHF_2CH_3 and CF_3CHFCF_3; and perfluorocarbons such as CF_3CF_3 and $CF_3CF_2CF_3$.

Where mixtures of the fluorocarbons or hydrogen-containing chlorofluorocarbons are employed they may be mixtures of the above identified compounds or mixtures, preferably binary mixtures, with other fluorocarbons or hydrogen-containing chlorofluorocarbons for example $CHClF_2$, CH_2F_2 and CF_3CH_3. Preferably a single fluorocarbon or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as propellants are C_{1-4}hydrogen-containing fluorocarbons such as 1,1,1,2-tetrafluoroethane(CF_3CH_2F) and 1,1,1,2,3,3,3-heptafluoro-n-propane (CF_3CHFCF_3).

It is desirable that the formulations of the invention contain no components which may provoke the degradation of stratospheric ozone. In particular it is desirable that the formulations are substantially free of chlorofluorocarbons such as CCl_3F, CCl_2F_2 and CF_3CCl_3.

The propellant may additionally contain a volatile adjuvant such as a saturated hydrocarbon for example propane, n-butane, isobutane, pentane and isopentane or a dialkyl ether for example dimethyl ether. In general, up to 50% w/w of the propellant may comprise a volatile hydrocarbon, for example 1 to 30% w/w. However, formulations which are substantially free of volatile adjuvants are preferred.

It is further desirable that the formulations of the invention are substantially free of liquid components of higher polarity than the propellant employed. Polarity may be determined for example, by the method described in European Patent Application Publication No. 0327777. In particular formulations which are substantially free of alcohols such as ethanol are preferable. As used herein "substantially free" means less than 1% w/w based upon the fluorocarbon or hydrogen-containing chlorofluorocarbon, in particular less than 0.5% for example 0.1% or less.

A particularly preferred embodiment of the invention provides a pharmaceutical aerosol formulation consisting essentially of one or more particulate medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof, and one or more fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

It will be appreciated by those skilled in the art that the aerosol formulations according to the invention may , if desired, contain a combination of two or more active ingredients. Aerosol compositions containing two active ingredients (in a conventional propellant system) are known, for example, for the treatment of respiratory disorders such as asthma. Accordingly the present invention further provides aerosol formulations in accordance with the invention which contain two or more particulate medicaments. Medicaments may be selected from suitable combinations of the medicaments mentioned hereinbefore or may be selected from any other suitable drug useful in inhalation therapy and which may be presented in a form which is substantially completely insoluble in the

selected propellant. Appropriate medicaments may thus be selected from, for example, analgesics, e.g. codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g. diltiazem; antiallergics, e.g. cromoglycate, ketotifen or nedocromil; antiinfectives e.g. cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g. methapyrilene; anti-inflammatories, e.g. flunisolide, budesonide, tipredane or triamcinolone acetonide; antitussives, e.g. noscapine; bronchodilators, e.g. ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, tulobuterol, orciprenaline, or (-)-4-amino-3,5-dichloro-α-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g. amiloride; anticholinergics e.g. ipratropium, atropine or oxitropium; hormones, e.g. cortisone, hydrocortisone or prednisolone; xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (e.g. as alkali metal or amine salts or as acid addition salts) or as esters (e.g. lower alkyl esters) or as solvates (e.g. hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Particularly preferred aerosol formulations contain salbutamol (e.g. as the free base or the sulphate salt) or salmeterol (e.g. as the xinafoate salt) in combination with an antiinflammatory steroid such as a beclomethasone ester (e.g. the diproprionate) or a fluticasone ester (e.g. the propionate) or an antiallergic such as cromoglycate (e.g. the sodium salt). Combinations of salmeterol and fluticasone propionate or beclomethasone dipropionate, or salbutamol and fluticasone propionate or beclomethasone dipropionate are preferred, especially salmeterol xinafoate and fluticasone propionate or salbutamol and beclomethasone dipropionate.

The formulations of the invention may be prepared by dispersal of the medicament in the selected propellant in an appropriate container, e.g. with the aid of sonication. The

process is desirably carried out under anhydrous conditions to obviate any adverse effects of moisture on suspension stability.

The formulations according to the invention form weakly flocculated suspensions on standing but, surprisingly, these suspensions have been found to be easily redispersed by mild agitation to provide suspensions with excellent delivery characteristics suitable for use in pressurised inhalers, even after prolonged storage. Minimising and preferably avoiding the use of formulation excipients e.g. surfactants, cosolvents etc in the aerosol formulations according to the invention is also advantageous since the formulations may be substantially taste and odour free, less irritant and less toxic than conventional formulations.

The chemical and physical stability and the pharmaceutical acceptability of the aerosol formulations according to the invention may be determined by techniques well known to those skilled in the art. Thus, for example, the chemical stability of the components may be determined by HPLC assay, for example, after prolonged storage of the product. Physical stability data may be gained from other conventional analytical techniques such as, for example, by leak testing, by valve delivery assay (average shot weights per actuation), by dose reproducibility assay (active ingredient per actuation) and spray distribution analysis.

The particle size distribution of the aerosol formulations according to the invention is particularly impressive and may be measured by conventional techniques, for example by cascade impaction or by the "Twin Impinger" analytical process. As used herein reference to the "Twin Impinger" assay means "Determination of the deposition of the emitted dose in pressurised inhalations using apparatus A" as defined in British Pharmacopaeia 1988, pages A204-207, Appendix XVII C. Such techniques enable the "respirable fraction" of the aerosol formulations to be calculated. As used herein reference to "respirable fraction" means the amount of active ingredient collected in the lower impingement chamber per actuation expressed as a percentage of the total amount of active ingredient delivered per actuation using the twin impinger method described above. The formulations according to the invention have been found to have a respirable fraction of

20% or more by weight of the medicament, preferably 25 to 70%, for example 30 to 60%.

Optionally, the medicament may be surface-modified prior to its dispersion in the propellant by treatment with a substantially non-polar liquid medium which is a non-solvent for the medicament. There is thus provided in a further aspect of the invention an aerosol formulation comprising particulate, surface-modified medicament, as defined herein, and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant. By "surface-modified medicament" is meant particles of medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof which have been surface-modified by admixture with a substantially non-polar non-solvent liquid, followed by removal of the liquid. The substantially non-polar non-solvent liquid medium is conveniently an aliphatic hydrocarbon, e.g. a lower alkane, which is sufficiently volatile to permit its ready evaporation, e.g. at ambient temperature and pressure, after slurrying with the medicament. The use of isopentane as liquid medium is particularly advantageous in this respect.

The medicament is desirably slurried with the liquid medium under anhydrous conditions to obviate any adverse effects of moisture on suspension stability. The slurry may advantageously be sonicated to maximise the surface-modifying effect of the treatment. The liquid may be removed by any convenient means for example by evaporation or by filtration followed by evaporation, provided that following treatment the medicament is substantially free of the liquid. The formulations of the invention will be substantially free of the non-solvent non-polar liquid. Surface-modified medicament prepared by the above-described process comprises a further aspect of the present invention.

The formulations according to the invention may be filled into canisters suitable for delivering pharmaceutical aerosol formulations. Canisters generally comprise a container capable of withstanding the vapour pressure of the propellant used such as a plastic or plastic-coated glass bottle or preferably a metal can, for example an aluminium can which

may optionally be anodised, lacquer-coated and/or plastic-coated, which container 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 and neoprene. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (e.g. DF10, DF30, DF60), Bespak plc, UK (e.g. BK300, BK356) and 3M-Neotechnic Ltd, UK (e.g. Spraymiser™).

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 aluminium can to form an empty canister. The particulate medicament is added to a charge vessel and liquified propellant is pressure filled through the charge vessel into a manufacturing vessel. The drug suspension is mixed before recirculation to a filling machine and an aliquot of the drug suspension is then filled through the metering valve into the canister. Typically, in batches prepared for pharmaceutical use, each filled canister is check-weighed, coded with a batch number and packed into a tray for storage before release testing.

Each filled canister is conveniently fitted into a suitable channelling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs or nasal cavity of a patient. Suitable channelling 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 nose or mouth of a patient e.g. a mouthpiece actuator. Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "puff", for example in the range of 10 to 5000 microgram medicament per puff.

Administration of medicament may be indicated for the treatment of mild, moderate or severe acute or chronic symptoms or for prophylactic treatment. It will be appreciated

that the precise dose administered will depend on the age and condition of the patient, the particular particulate medicament used and the frequency of administration and will ultimately be at the discretion of the attendant physician. When combinations of medicaments are employed the dose of each component of the combination will in general be that employed for each component when used alone. Typically, administration may be one or more times, for example from 1 to 8 times per day, giving for example 1,2,3 or 4 puffs each time.

Suitable daily doses, may be, for example in the range 50 to 200 microgram of salmeterol, 100 to 1000 microgram of salbutamol, 50 to 2000 microgram of fluticasone propionate or 100 to 2000 microgram of beclomethasone dipropionate, depending on the severity of the disease.

Thus, for example, each valve actuation may deliver 25 microgram salmeterol, 100 microgram salbutamol, 25, 50, 125 or 250 microgram fluticasone propionate or 50, 100, 200 or 250 microgram beclomethasone dipropionate. Typically each filled canister for use in a metered dose inhaler contains 100, 160 or 240 metered doses or puffs of medicament.

The filled canisters and metered dose inhalers described herein comprise further aspects of the present invention.

A still further aspect of the present invention comprises a method of treating respiratory disorders such as, for example, asthma, which comprises administration by inhalation of an effective amount of a formulation as herein described.

The following non-limitative Examples serve to illustrate the invention.

Example 1

Micronised salmeterol xinafoate (24mg) was weighed into a clean, dry, plastic-coated glass bottle and 1,1,1,2-tetrafluoroethane (18.2g) was added from a vacuum flask. The bottle was quickly sealed with a blank aluminium ferrule. The resulting aerosol contained 0.132% $^{w}/_{w}$ salmeterol xinafoate.

Example 2

Micronised salmeterol xinafoate (38.28g) and 1,1,1,2-tetrafluoroethane (36.36kg) were added to a pressure vessel and mixed with a high shear mixer for 20 minutes. Aliquots (18.2g) of the suspension were filled into aluminium cans closed with a metering valve, filling under pressure through the valve using conventional filling equipment. The resulting inhalers contained 9.57mg salmeterol xinafoate and delivered 25 microgram salmeterol (39.9 microgram salt) per actuation.

Example 3

Micronised fluticasone propionate (24mg) was weighed into a clean, dry, plastic-coated glass bottle and 1,1,1,2-tetrafluoroethane (18.2g) was added from a vacuum flask. The bottle was quickly sealed with a blank aluminium ferrule. The resulting aerosol contained 0.132% $^{w}/_{w}$ fluticasone propionate.

Examples 4 and 5

Micronised fluticasone propionate (66mg or 6.6mg) was weighed directly into each of 100 open aluminium cans and a metering valve was then crimped into place on each can. 1,1,1,2-Tetrafluoroethane (18.2g) was then added to each canister under pressure, through the valve, and each filled canister shaken to disperse the drug. The resulting inhalers contained 66 or 6.6mg fluticasone propionate and delivered 250 or 25 microgram fluticasone propionate per actuation (Examples 4 and 5 respectively).

Example 6

Micronised salbutamol (24mg) was weighed into a clean, dry, plastic-coated glass bottle and 1,1,1,2-tetrafluoroethane (18.2g) was added from a vacuum flask. The bottle was quickly sealed with a blank aluminium ferrule. The resulting aerosol contained 0.132% $^{w}/_{w}$ salbutamol.

Examples 7 and 8

Micronised salbutamol (24mg or 48mg) was weighed directly into each of 3 open aluminium cans. 1,1,1,2-Tetrafluoroethane (18.2g) was added to each can from a vacuum flask and a metering valve was then crimped into place. Each filled canister was then shaken in an ultrasonic bath for 8 minutes. The resulting inhalers contained 24mg or 48mg salbutamol and delivered 100 or 200 microgram salbutamol per actuation (Examples 7 and 8 respectively).

Example 9

Micronised salbutamol sulphate (31.7mg) was weighed into a clean, dry, plastic-coated glass bottle and 1,1,1,2-tetrafluoroethane (18.2g) was added from a vacuum flask. The bottle was quickly sealed with a blank aluminium ferrule. The resulting aerosol contained 0.174% $^{w}/_{w}$ salbutamol sulphate.

Example 10

Micronised salbutamol sulphate (31.7mg) was weighed directly into each of 4 open aluminium cans. 1,1,1,2-Tetrafluoroethane (18.2g) was added to each can from a vacuum flask and a metering valve was then crimped into place. Each filled canister was then shaken in an ultrasonic bath for 5 minutes. The resulting inhalers contained 31.7mg salbutamol sulphate and delivered 100 microgram salbutamol per actuation.

Example 11

Isopentane (25ml) was added to micronised salmeterol xinafoate (0.5g) to form a slurry, which was sonicated for 3 minutes. The resulting suspension was dried by evaporating the isopentane at ambient temperature to yield surface-modified salmeterol xinafoate. Samples of this product (11.6mg) were weighed into aluminium aerosol cans and 1,1,1,2-tetrafluoroethane (18.2g - 99.95% w/w of total fill weight) was added to each can, whereafter suitable metering valves were crimped onto the cans, which were then each sonicated for 5 minutes. The resulting aerosols contained salmeterol in an amount equivalent to 240 actuations at 25 microgram per actuation.

Example 12

Micronised beclomethasone dipropionate monohydrate (68 mg) was weighed into a clean, dry, plastic-coated glass bottle and 1,1,1,2-tetrafluoroethane (to 18.2g) was added from a vacuum flask. The bottle was quickly sealed with a metering valve. The resulting aerosol dispensed 250 microgram beclomethasone dipropionate (as the monohydrate) per 75.8mg actuation.

Example 13

Micronised salmeterol xinafoate (9.57mg) is weighed directly into an aluminium can and 1,1,1,2,3,3,3-heptafluoro-n-propane (to 21.4g) added from a vacuum flask. A metering valve is crimped into place and the filled canister sonicated for five minutes. The aerosol delivers 25 microgram salmeterol per actuation.

Example 14

Micronised fluticasone propionate (13.3mg) is weighed directly into an aluminium can and 1,1,1,2,3,3,3-heptafluoro-n-propane (to 21.4g) added from a vacuum flask. A metering valve is crimped into place and the filled canister sonicated for five minutes. The aerosol delivers 50 microgram fluticasone propionate per actuation.

Example 15

Micronised salbutamol sulphate (29mg) was weighed directly into an aluminium can and 1,1,1,2,3,3,3-heptafluoro-n-propane (to 21.4g) added from a vacuum flask. A metering valve was crimped into place and the filled canister sonicated for five minutes. The aerosol delivered 100 microgram salbutamol per actuation.

Example 16

Micronised beclomethasone diproprionate monohydrate (62mg) was weighed directly into an aluminium can and 1,1,1,2,3,3,3-heptafluoro-n-propane (to 21.4g) added from a vacuum flask. A metering valve was crimped into place and the filled canister sonicated

for five minutes. The aerosol delivered 250 microgram beclomethasone diproprionate per actuation.

Example 17

	Per Inhaler % w/w	Per Actuation
Salmeterol xinafoate	0.048	36.25 microgram
Fluticasone propionate	0.066	50 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

Micronised medicaments were weighed into an aluminium can, 1,1,1,2-tetrafluoroethane (18.2g) was added from a vacuum flask and a metering valve was crimped into place.

Example 18

	Per Inhaler % w/w	Per Actuation
Salmeterol xinafoate	0.048	36.25 microgram
Fluticasone propionate	0.165	125 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

Micronised medicaments were weighed into an aluminium can, 1,1,1,2-tetrafluoroethane (18.2g) was added from a vacuum flask and a metering valve was crimped into place.

Example 19

	Per Inhaler % w/w	Per Actuation
Salmeterol xinafoate	0.048	36.25 microgram
Fluticasone propionate	0.132	100 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

Example 20

	Per Inhaler % w/w	Per Actuation
Salmeterol xinafoate	0.048	36.25 microgram
Fluticasone propionate	0.330	250 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

Example 21

	Per Inhaler % w/w	Per Actuation
Salbutamol *	0.132	100 microgram
Fluticasone propionate	0.132	100 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

* as free base or an equivalent weight of salt e.g. sulphate

Example 22

	Per Inhaler % w/w	Per Actuation
Salbutamol *	0.264	200 microgram
Fluticasone propionate	0.330	250 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

* as free base or an equivalent weight of salt e.g. sulphate

Example 23

	Per Inhaler % w/w	Per Actuation
Salmeterol xinafoate	0.048	36.25 microgram
Beclomethasone dipropionate	0.066	50 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

Example 24

	Per Inhaler % w/w	Per Actuation
Salmeterol xinafoate	0.048	36.25 microgram
Fluticasone propionate	0.264	200 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

Example 25

	Per Inhaler % w/w	Per Actuation
Salbutamol *	0.132	100 microgram
Beclomethasone dipropionate	0.066	50 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

* as free base or an equivalent weight of salt e.g. sulphate

Example 26

	Per Inhaler % w/w	Per Actuation
Salbutamol *	0.264	200 microgram
Beclomethasone dipropionate	0.264	200 microgram
1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

* as free base or an equivalent weight of salt e.g. sulphate

In Examples 19 to 26 micronised medicaments are weighed into aluminium cans, 1,1,1,2-tetrafluoroethane (18.2g) is added from a vacuum flask, and metering valves are crimped into place.

CLAIMS

1. A pharmaceutical aerosol formulation which comprises particulate medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant.

2. A pharmaceutical aerosol formulation which comprises particulate medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant and with the proviso that when said formulation consists essentially of salbutamol and 1,1,1,2-tetrafluoroethane in a weight ratio of 0.05:18, said salbutamol is present in the form of a physiologically acceptable salt.

3. A pharmaceutical aerosol formulation consisting essentially of one or more particulate medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof, and one or more fluorocarbon or hydrogen-containing chlorofluorocarbon propellant.

4. A formulation as claimed in any one of claims 1 to 3 wherein the medicament is salmeterol xinafoate.

5. A formulation as claimed in any one of claims 1 to 3 wherein the medicament is salbutamol sulphate.

6. A formulation as claimed in any one of claims 1 to 3 wherein the medicament is fluticasone propionate.

7. A formulation as claimed in any one of claims 1 to 3 wherein the medicament is beclomethasone dipropionate or a physiologically acceptable solvate thereof.

8. A formulation as claimed in one of claims 1 to 7 wherein the propellant comprises 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane.

9. A formulation as claimed in one of claims 1 to 8 wherein the propellant comprises 1,1,1,2-tetrafluoroethane.

10. A formulation as claimed in any one of claims 1 to 9 wherein the medicament is present in an amount of 0.005 to 10% w/w based on the total weight of the formulation.

11. A formulation as claimed in any one of claims 1 to 10 which contains two or more particulate medicaments.

12. A formulation as claimed in Claim 11 which contains salbutamol or salmeterol or a physiologically acceptable salt thereof in combination with an antiinflammatory steroid or an antiallergic.

13. A formulation as claimed in Claim 12 which contains salmeterol or salbutamol or a physiologically acceptable salt thereof in combination with fluticasone propionate or beclomethasone dipropionate or a physiologically acceptable solvate thereof.

14. A formulation as claimed in Claim 13 which contains salmeterol xinafoate and fluticasone propionate.

15. A formulation as claimed in Claim 13 which contains salbutamol and beclomethasone dipropionate.

16. A formulation as claimed in any one of claims 1 to 15 which has a respirable fraction of 20% or more by weight of the medicament.

17. A formulation as claimed in any one of claims 1 to 16 wherein said particulate medicament is surface-modified.

18. Surface-modified medicament prepared by admixture of particles of a medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof, with a substantially non-polar, non-solvent liquid, followed by removal of the liquid.

19. A canister suitable for delivering a pharmaceutical aerosol formulation which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically acceptable salts and solvates thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant.

20. A canister as claimed in claim 19 wherein the container is a metal can.

21. A metered dose inhaler which comprises a canister as claimed in claim 19 or claim 20 fitted into a suitable channelling device.

22. A method of treating respiratory disorders which comprises administration by inhalation of an effective amount of a pharmaceutical aerosol formulation which comprises particulate medicament selected from the group consisting of salmeterol, salbutamol, fluticasone propionate, beclomethasone dipropionate and physiologically

acceptable salts and solvates thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon propellant, which formulation is substantially free of surfactant.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/02808

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	WO,A,9 111 496 (BOEHRINGER INGELHEIM) 8 August 1991 see claims	1-22
A	WO,A,9 111 173 (FISONS) 8 August 1991 cited in the application see claims see page 3, line 15 - line 16 see page 7, line 19 - line 20 see page 8, line 1 - line 7	1-22
P,A	WO,A,9 208 447 (GLAXO) 29 May 1992 see claims	1-22

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 MARCH 1993	01. 04. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 92/ 02808

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
ALTHOUGH CLAIM 22 IS DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN BODY BY THERAPY (RULE 39.1(IV)) THE SEARCH HAS BEEN CARRIED OUT AND BASED UPON THE ALLEGED EFFECTS OF THE COMPOSITION.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9202808
SA 67632

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 10/03/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9111496	08-08-91	DE-A-	4003270	08-08-91
		AU-A-	7211691	21-08-91
		EP-A-	0513099	19-11-92
WO-A-9111173	08-08-91	EP-A-	0513127	19-11-92
WO-A-9208447	29-05-92	AU-A-	8862991	11-06-92