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(54) Titre : MEDICAMENTS EN AEROSOL AVEC PROPULSEUR CONTENANT UN HYDROCARBURE FLUORE
(54) Title: FLUOROCARBON AEROSOL MEDICAMENTS

(57) Abrégé/Abstract:
A pharmaceutical aerosol formulation for use for the administration of medicaments by inhalation consists essentially of particulate salmeterol xinafoate as medicament and 1,1,1,2-tetrafluoroethane as propellant, the formulation is free of surfactant, and the medicament is present in an amount of 0.01 to 1% w/w relative to the total weight of the formulation. There is also provided a process for preparing a filled pharmaceutical aerosol canister which comprises: preparing a formulation of the invention and filling the formulation into a can which is closed with a metering valve. The formulation may be used for the manufacture of a medicament for administration by inhalation for the treatment of respiratory disorders such as asthma.

ABSTRACT

A pharmaceutical aerosol formulation for use for the administration of medicaments by inhalation consists essentially of particulate salmeterol xinafoate as medicament and 1,1,1,2-tetrafluoroethane as propellant, the formulation is free of surfactant, and the medicament is present in an amount of 0.01 to 1% w/w relative to the total weight of the formulation. There is also provided a process for preparing a filled pharmaceutical aerosol canister which comprises: preparing a formulation of the invention and filling the formulation into a can which is closed with a metering valve. The formulation may be used for the manufacture of a medicament for administration by inhalation for the treatment of respiratory disorders such as asthma.

FLUOROCARBON AEROSOL MEDICAMENTS

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

This application is a division of Canadian Application 2,447,510, filed December 4, 1992.

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 WO 91/11173, WO 91/11495, and WO 91/14422 are concerned with formulations comprising an admixture of drug and surfactant, WO 91/04011 discloses medicinal aerosol formulations in which the particulate medicaments are pre-coated with surfactant prior to dispersal in 1,1,1,2-tetrafluorethane.

It has now surprisingly been 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-tetrafluorethane 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.

In accordance with one aspect of the invention, there is provided a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists essentially of particulate salmeterol xinafoate as medicament and 1,1,1,2-tetrafluoroethane as propellant, and that the formulation is free of surfactant.

In another aspect of the invention, there is provided a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterized in that it consists of particulate salmeterol xinafoate as medicament and 1,1,1,2-tetrafluoroethane as propellant.

In accordance with another aspect of the invention, there is provided 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 of the invention as described hereinbefore.

In another aspect of the invention, there is provided a process for preparation of a formulation of the invention as described hereinbefore, which comprises dispersing the medicament in the propellant.

In yet another aspect of the invention, there is provided a process for preparing a filled pharmaceutical aerosol canister which comprises:

(a) preparing a formulation of the invention as described hereinbefore; and

(b) filling the formulation into an aluminium can which is closed with a metering valve.

In another aspect of the invention, there is provided a filled pharmaceutical aerosol canister obtained by the filling process of the invention.

In still another aspect of the invention, there is provided a process for preparing a metered dose inhaler which comprises fitting a filled canister of the invention into a channelling device.

In yet another aspect of the invention, there is provided a metered dose inhaler obtainable by the aforementioned process.

In yet another aspect of the invention, there is provided the use of a pharmaceutical aerosol formulation characterized in that it consists essentially of particulate salmeterol xinafoate as medicament, and 1,1,1,2-tetrafluoroethane as propellant, and that the formulation is free of surfactant, for the manufacture of a medicament for administration by inhalation in the treatment of asthma.

In still another aspect of the invention, there is provided the use of pharmaceutical aerosol formulation characterized in that it consists of particulate salmeterol xinafoate and 1,1,1,2-tetrafluoroethane, for the manufacture of a medicament for administration by inhalation in the treatment of asthma.

There is also disclosed herein 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.

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 described herein 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, preperably 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 formulation described herein may be any fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof having a sufficient vapour pressure to render them effective as propellants. Preferably the propel-lant 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.

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 process for preparing a filled pharmaceutical aerosol canister which comprises:

(a) preparing a pharmaceutical aerosol formulation for use in the administration of a medicament by inhalation characterised in that it consists essentially of particulate salmeterol xinafoate having a particles size of less than 100 microns and 1,1,1,2-tetrafluoroethane as propellant, which formulation contains less than 0.0001% w/w surfactant based on weight of the medicament; and

(b) filling the formulation into an aluminium can which is closed with a metering valve.

2. A process according to claim 1, wherein the formulation consists of particulate salmeterol xinafoate having a particle size of less than 100 microns and 1,1,1,2-tetrafluoroethane as propellant.

3. A process according to claim 1 or 2, wherein in step (a) the formulation is prepared by dispersing the medicament in the propellant.

4. A process according to any one of claims 1 to 3, wherein in step (b) the metering valve is crimped onto the aluminium can to form an empty canister and an aliquot of the formulation is filled through the metering valve into the canister.

5. A process according to claim 1 which comprises:

(i) crimping the metering valve onto the aluminium can to form an empty canister;

(ii) adding particulate medicament to a charge vessel and pressure filling liquefied propellant through the charge vessel into a manufacturing vessel to form a drug suspension;

(iii) mixing the drug suspension before recirculation to a filling machine; and

(iv) filling an aliquot of the drug suspension through the metering valve into the canister.

6. A process according to any one of claims 1 to 5, wherein the aluminium can is anodised, lacquer coated and/or plastic coated.

7. A filled pharmaceutical aerosol canister obtained by the process according to any one of claims 1 to 6.

8. A process for preparing a metered dose inhaler which comprises fitting a canister according to claim 7 into a suitable channelling device.

9. A process according to claim 8, wherein the channelling device comprises a valve actuator.

10. A metered dose inhaler obtained by the process of claim 8 or 9.