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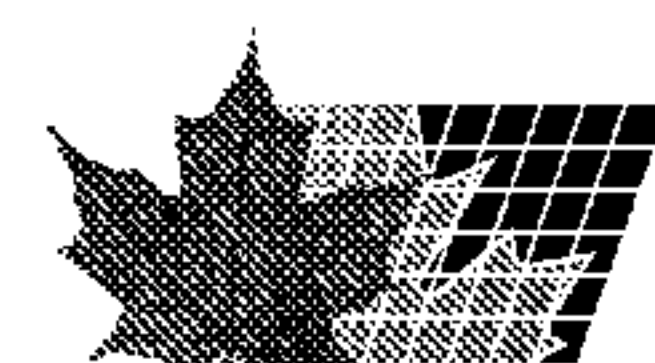
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(54) Title: FLUOROCARBON AEROSOL MEDICAMENTS

(57) **Abrégé/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.



ABSTRACT

5 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
10 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.

FLUOROCARBON AEROSOL MEDICAMENTS

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

This application is a divisional of Canadian Application 2,362,539, filed December 4, 1992.

10 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 ($\text{CF}_2\text{ClCF}_2\text{Cl}$) 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.

20 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.

30 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.

10 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

20 dispersions may be formed where the medicament is selected from fluticasone propionate and salmeterol and physiologically acceptable salts thereof.

There is thus provided in one aspect of the invention a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists essentially of particulate medicament which is salmeterol or a physiologically acceptable salt thereof and fluticasone propionate in combination and 1,1,1,2-tetrafluoroethane as propellant, and that the formulation is free of surfactant, wherein said formulation contains medicament in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.

In another aspect of the invention there is provided a pharmaceutical

30 aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists of particulate medicament which is salmeterol or a physiologically acceptable salt thereof and fluticasone propionate in combination and 1,1,1,2-tetrafluoroethane as propellant, wherein said formulation contains

medicament in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.

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 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, C₁₋₄hydrogen-containing chlorofluorocarbons such as CH₂ClF, CCIF₂CHClF, CF₃CHClF, CHF₂CCIF₂, CHClFCHF₂, CF₃CH₂Cl and CCIF₂CH₃; C₁₋₄hydrogen-containing fluorocarbons such as CHF₂CHF₂, CF₃CH₂F, CHF₂CH₃ and CF₃CHF₂CF₃; and perfluorocarbons such as CF₃CF₃ and CF₃CF₂CF₃.

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 CHClF₂, CH₂F₂ and

CF₃CH₃. Preferably a single fluorocarbon or hydrogen-containing chlorofluorocarbon is employed as the propellant. Particularly preferred as propellants are C₁₋₄hydrogen-containing fluorocarbons such as 1,1,1,2-tetrafluoroethane(CF₃CH₂F) and 1,1,1,2,3,3,3-heptafluoro-n-propane (CF₃CHFCF₃).

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 CCl₃F, CCl₂F₂ and CF₃CCl₃.

10 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.

Aerosol compositions containing two active ingredients (in a conventional propellant system) are known, for example, for the treatment of respiratory
20 disorders such as asthma.

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.
30 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.

10 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 Pharmacopoeia 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
20 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
30 medicament selected from the group consisting of fluticasone propionate and salmeterol and physiologically acceptable salts 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 slurring 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), Bepak plc, UK (e.g. BK300, BK356) and 3M-Neotechnic Ltd, UK (e.g. SpraymiserTM).

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
10 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
20 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
30 salmeterol, or 25, 50, 125 or 250 microgram fluticasone propionate. 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

		Per Inhaler % w/w	Per Actuation
10	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 2

		Per Inhaler % w/w	Per Actuation
	Salmeterol xinafoate	0.048	36.25 microgram
	Fluticasone propionate	0.165	125 microgram
20	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 3

	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 4

	Per Inhaler % w/w	Per Actuation
Salmeterol xinafoate	0.048	36.25 microgram
Fluticasone propionate	0.330	250 microgram
10 1,1,1,2-Tetrafluoroethane	to 100	to 75.8mg

Example 5

	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

In Examples 3 to 5 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 for use in the administration of medicaments by inhalation characterised in that it consists essentially of particulate medicament which is salmeterol or a physiologically acceptable salt thereof and fluticasone propionate in combination and 1,1,1,2-tetrafluoroethane as propellant, and that the formulation is free of surfactant, wherein said formulation contains medicament in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.
2. A pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists of particulate medicament which is salmeterol or a physiologically acceptable salt thereof and fluticasone propionate in combination and 1,1,1,2-tetrafluoroethane as propellant, wherein said formulation contains medicament in an amount of 0.01 to 1% w/w relative to the total weight of the formulation.
3. A pharmaceutical aerosol formulation as claimed in claim 1 or claim 2 wherein salmeterol is present as the xinafoate salt.
4. A pharmaceutical aerosol formulation according to claim 3 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.66% w/w.
5. A pharmaceutical aerosol formulation according to claim 3 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.165% w/w.
6. A pharmaceutical aerosol formulation according to claim 3 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.132% w/w.
7. A pharmaceutical aerosol formulation according to claim 3 wherein salmeterol xinafoate is present in the formulation at a concentration of

0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.330% w/w.

8. A pharmaceutical aerosol formulation according to claim 3 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.264% w/w.
9. A pharmaceutical aerosol formulation according to any one of claims 1 to 8 wherein the use is use in the treatment of respiratory disorders.
10. A pharmaceutical aerosol formulation according to claim 9 wherein the respiratory disorder is asthma.
11. The use of a pharmaceutical aerosol formulation according to any one of claims 1 to 8 for the manufacture of a medicament for administration by inhalation for the treatment of respiratory disorders.
12. The use of a pharmaceutical aerosol formulation according to claim 11 wherein said respiratory disorder is asthma.
13. A canister comprising a container closed with a metering valve which contains a pharmaceutical aerosol formulation according to any one of claims 1 to 10.
14. A canister according to claim 13 wherein the container is an aluminium can.
15. A canister according to claim 14 wherein the aluminium can is anodised, lacquer coated and/or plastic coated.
16. A metered dose inhaler which comprises a canister according to any of claims 13 to 15 fitted into a suitable channelling device.
17. A process for the preparation of a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists essentially of particulate medicament which is salmeterol or a physiologically acceptable salt thereof and fluticasone propionate in combination and 1,1,1,2-tetrafluoroethane as propellant, and that the

formulation is free of surfactant, wherein said formulation contains medicament in an amount of 0.01% to 1% w/w relative to the total weight of the formulation, which process comprises dispersing the medicament in the propellant.

18. A process for the preparation of a pharmaceutical aerosol formulation for use in the administration of medicaments by inhalation characterised in that it consists of particulate medicament which is salmeterol or a physiologically acceptable salt thereof and fluticasone propionate in combination and 1,1,1,2-tetrafluoroethane as propellant, wherein said formulation contains medicament in an amount of 0.01% to 1% w/w relative to the total weight of the formulation, which process comprises dispersing the medicament in the propellant.
19. A process as claimed in claim 17 or claim 18 wherein salmeterol is present as the xinafoate salt.
20. A process according to claim 19 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.066% w/w.
21. A process according to claim 19 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.165% w/w.
22. A process according to claim 19 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.132% w/w.
23. A process according to claim 19 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.330% w/w.
24. A process according to claim 19 wherein salmeterol xinafoate is present in the formulation at a concentration of 0.048% w/w and fluticasone propionate is present in the formulation at a concentration of 0.264% w/w.