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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 salmeterol and physiologically acceptable salts and solvates thereof and an anticholinergic medicament in combination, and a propellant which is 1,1,1,2-tetrafluoroethane, 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, as well as a canister for delivery of the formulation.

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 salmeterol and physiologically acceptable salts and solvates thereof and an anticholinergic medicament in combination, and a propellant which is 1,1,1,2-tetrafluoroethane, 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, as well as a canister for delivery of the formulation.

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 2,303,685, 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 minimize 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.

In accordance with one aspect of the invention, there is provided a pharmaceutical aerosol formulation which consists essentially of, or consists of, particulate medicament having a particle size of less than 100 microns which is salmeterol or a salt or solvate thereof and an anticholinergic medicament in combination and 1,1,1,2-tetrafluoroethane as propellant, wherein the formulation contains 0.01 to 1% of medicament relative to the total weight of the formulation, which formulation contains less than 0.0001% of surfactant.

In 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 which container is closed with a metering valve and contains a pharmaceutical aerosol formulation according to the invention as described hereinbefore.

In still another aspect of the invention, there is provided use of a formulation of the invention, as described hereinbefore, for the manufacture of a medicament for the treatment of respiratory disorders.

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

In still yet another aspect of the invention, there is provided a metered dose inhaler which comprises a canister of the invention, as described hereinbefore, fitted into a suitable channeling device.

There is also disclosed 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.

There is further disclosed 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 inventions 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 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 described herein 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 (-)-

Claims

1. A pharmaceutical aerosol formulation which consists essentially of particulate medicament having a particle size of less than 100 microns which is salmeterol or a salt or solvate thereof and an anticholinergic medicament in combination and 1,1,1,2-tetrafluoroethane as propellant, wherein the formulation contains 0.01 to 1% of medicament relative to the total weight of the formulation, which formulation contains less than 0.0001% of surfactant.

2. A pharmaceutical aerosol formulation which consists of particulate medicament having a particle size of less than 100 microns which is salmeterol or a salt or solvate thereof and an anticholinergic medicament in combination and 1,1,1,2-tetrafluoroethane as propellant, wherein the formulation contains 0.01 to 1% of medicament relative to the total weight of the formulation, which formulation contains less than 0.0001% of surfactant.

3. A formulation as claimed in claim 1 or claim 2 wherein salmeterol is present as the xinafoate salt.

4. A formulation as claimed in any one of claims 1 to 3 wherein the anticholinergic medicament is selected from the list consisting of ipatropium, atropine, oxitropium and salts thereof.

5. A formulation as claimed in claim 4 wherein the anticholinergic medicament is ipratropium or a salt thereof.

6. A formulation according to any one of claims 1 to 5 wherein the medicament is present in an amount of 0.1 to 1% w/w based on the weight of formulation.

7. A canister suitable for delivering a pharmaceutical aerosol formulation which comprises a container capable of withstanding the vapour pressure of the propellant which container is closed with a metering valve and contains a pharmaceutical aerosol formulation according to any one of claims 1 to 6.

8. A canister according to claim 7 wherein the container is a metal can.

9. A canister according to claim 8 wherein the container is an aluminium can which is optionally anodised, lacquer coated and/or plastics coated.

10. Use of a formulation according to any one of claims 1 to 6 for the manufacture of a medicament for the treatment of respiratory disorders.

11. A process for preparing a pharmaceutical formulation according to any one of claims 1 to 6 which comprises dispersing the medicament in the propellant.

12. A metered dose inhaler which comprises a canister according to any one of claims 7 to 9 fitted into a suitable channelling device.