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Formulation for a metered dose inhaler using hydro-fluoro-alkanes as propellants

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(54) Title: FORMULATION FOR A METERED DOSE INHALER USING HYDRO-FLUORO-ALKANES AS PROPELLANTS

(57) Abstract: An improved suspension formulation for use in a metered-dose inhaler having a hydro-fluoro-alkane propellant is described, the improvement being the controlled addition of a small quantity of water.

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Formulation for a Metered Dose Inhaler Using Hydro-Fluoro-Alkanes as Propellants

Application Data

This application claims benefit to US provisional application no. 60/456,113 filed 03/20/2003.

Background of the Invention

The physical stability (particle size growth, flocculation rate, sedimentation/creaming behaviors) of a non-aqueous based suspension metered dose inhaler (MDI) formulation is a critical factor that affects the pharmaceutical performance characteristics of the drug product. For a suspension MDI, the key pharmaceutical performance characteristics of the formulation include reproducible dosing, ready dispersibility of the suspended medicament, and minimal particle size change over time.

Water has long been considered to have a negative impact on the physical stability of non-aqueous suspensions. In the literature, the following two aspects are well established:

a) too much water results in altered sedimentation characteristics leading to fast sedimentation and therefore to variability in dose of the suspended active ingredient, and

b) too much water can alter the particle size distribution by contributing to the formation of flocculates and aggregates of the individual drug particles or can cause solubilizing and re-crystallizing of drug particles.

Summary of the Invention

Therefore in one aspect, the present invention advantageously provides a formulation wherein the amount of water is about 0.13 to about 0.18 percent (w/w) of the product formulation.

In another aspect, the present invention advantageously provides a meter dose inhaler containing the formulation according to the invention.

In a further aspect, the present invention advantageously provides a process of making a formulation according to the invention.

Detailed Description of the Preferred Embodiments

The inventors have determined that a minimum amount of water is needed to ensure adequate re-dispersion of the suspended active ingredient. The term "product formulation" shall be understood to mean all components as described herein contained in the metered dose inhaler. It shall be appreciated by the skilled artisan that this amount of water (w/w) of the product formulation is the final volume, and that one or more of the components may already possess water. The amount of water to add to achieve the desired amount in the product formulation can be determined without undue experimentation by those of ordinary skill in the art from the teachings in this application and from methods known in the art. Preferably, the amount of water is 0.16 %w/w of the product formulation. In this case, it has been found by the inventors of this application that adding about 0.13% or 0.14% of water to the other components as shown in the tables below achieves the preferred amount.

If the active ingredient is not readily re-dispersible, then, after a period of non-use by the patient, the amount of active ingredient per actuation will not be on target (either super-potent or sub-potent). The addition of specific amounts of water can aid in the ready re-dispersibility of the active ingredient in the metering chamber. This finding has been established for a suspension/solution formulation for use in a metered dose inhaler using an hydro-fluoro-alkane (HFA) as propellant. Specifically, a formulation comprising albuterol sulfate and ipratropium bromide, together with various other excipients and carriers, is described, using the HFA known in the industry as 134a.

Suitable excipients will be apparent to those of ordinary skill in the art. These include, but are not limited to: organic acids such as citric acid, lubricants such as oleic acid, ethanol and carriers.

Suitable carriers will be apparent to those of ordinary skill in the art. These include, but are not limited to: soy lecithin, polyvinylpyrollidones, organic polymers, phospholipids.

There are various MDI publications in the literature including US Publications 2003/0066525, 2003/0089368, US2001031244, US2003089369, US2003190287, US2003206870, US Patent nos. 5,225,183, 5,919,435, 6,306,368, 5,836,299, 6,092,696,

6,234,362, 6,036,942, 5,682,875, 6,305,371, and PCT publications WO 95/02651, WO 97/01611,WO 03/002169, WO 00/30607, WO 00/30608 and WO 98/56349 and EP 1 241 113, many deal with all aspects of HFA formulations. The inventors are not aware of any formulation patent publications for suspension MDIs that requires or recommends water to be added to the formulation to enhance performance.

Therefore, in one embodiment there is provided:
a formulation comprising
water in an amount of about 0.13 to about 0.18 percent (w/w) of the product formulation,
at least one HFA as a propellant,
one or more active ingredients, and
one or more excipients.

In another embodiment there is provided:
a formulation comprising
water in an amount of about 0.13 to about 0.18 percent (w/w) of the product formulation,
at least one HFA as a propellant,
albuerol sulfate,
ipratropium bromide, and
one or more excipients.

In a further embodiment there is provided:
a formulation comprising
water in an amount of about 0.13 to about 0.18 percent (w/w) of the product formulation,
at least one HFA as a propellant,
one or more excipients, and
active ingredients albuterol sulfate and ipratropium bromide, wherein the active ingredients of the formulation are suspended.

Below are three tables showing formulations incorporating the invention, that is, the deliberate addition of water to a formulation to be used in an MDI using at least one HFA as a propellant. The first two tables provide specific details for such formulation having albuerol sulfate and ipratropium bromide as active ingredients. The first table provides the formulation with no canister overfill.

Table 1

COMPONENT	MASS PER CAN	PERCENT
Albuterol Sulphate (micronized)	0.0240g	0.208
Ipratropium Bromide (monohydrate)	0.0042g	0.036
Ethanol (dehydrated, USP)	1.153g	10
Water	0.0150g	0.13
Polyvinylpyrrolidone (PVP, K-25)	0.0058g	0.050
Citric Acid (anhydrous)	0.0005g	0.004
HFA 134a (1,1,1,2-tetrafluoroethane)	10.3285g	89.542
TOTAL	**11.5310g**	**100**

The second table provides the same albuterol sulfate and ipratropium bromide formulation with a projected canister overfill included.

Table 2

COMPONENT	MASS PER CAN	PERCENT
Albuterol Sulphate (micronized)	0.0309g	0.208
Ipratropium Bromide (monohydrate)	0.0054g	0.036
Ethanol (dehydrated, USP)	1.482g	10
Water	0.0193g	0.13

Polyvinylpyrrolidone (PVP, K-25)	0.0074g	0.050
Citric Acid (anhydrous)	0.0006g	0.004
HFA 134a (1,1,1,2-tetrafluoroethane)	13.2744g	89.542
TOTAL	**14.32g**	**100**

The third table provides expected ranges for an albuterol sulfate/ipratropium bromide formulation according to the present invention.

Table 3

COMPONENT	MASS PER CAN	PERCENT
Albuterol Sulphate (micronized)	0.0240g 0.0216 – 0.0264 (+/-10%)	0.208
Ipratropium Bromide (monohydrate)	0.0042g 0.0038 – 0.0046 (+/-10%)	0.036
Ethanol (dehydrated, USP)	1.153g	10
Polyvinylpyrrolidone (PVP, K-25)	0.0058g 0.0049g – 0.0067g (+/-15%)	0.050
Citric Acid (anhydrous)	0.0005g	0.004
HFA 134a (1,1,1,2-tetrafluoroethane) and/or HFA 227	10.325g	89.542
TOTAL	**11.5125g**	**100**

There is a need to address the problem of actuation variability in formulations used in MDIs having at least one HFA as propellant where:

a) the formulation has a suspended, solid medicament and

b) the valve is designed to include a metering chamber, that is an area for the formulation to be dosed or dispensed to reside between actuations or dosings.

Provided these two conditions are met, there is the potential that the addition of a small, controlled amount of water can improve the redispersibility of the formulation in the metering chamber. This possibility exists regardless of whether the formulation is a "pure" suspension, that is, no drug or active ingredient is dissolved in the formulation. This possibility is also independent of the solid medicament, the stabilizing agent (if one is used), the propellants used or the type of co-solvent, if any, used.

Therefore, in another embodiment of the invention, there is provided a metered dose inhaler comprising

a formulation as described herein above wherein the albuterol sulfate, and the ipratropium bromide of the formulation is suspended;

a valve containing a metering chamber that is an area for the formulation to be dosed or dispensed to reside between actuations or dosings.

In yet another embodiment of the invention, there is provided a process of making a formulation as desribed herein above, comprising:

preparing a concentrate by adding :

ethanol, citric acid, ipratropium bromide monohydrate, polyvinylpyrrolidone and albuterol sulfate;

preparing a propellant, ethanol and water mixture, said mixture containing:

propellant HFA 134a,

a mixture of ethanol and water;

adding the concentrate to the mixture of propellant-ethanol-water to provide the formulation.

A formulation according to the present invention can be made as follows:

1. Concentrate Preparation

Prepare Concentrate with:

Ethanol,
Citric acid
Ipratropium bromide monohydrate
PVP
Albuterol Sulfate

Do not add water.

2. Dispensing of Propellant, Ethanol and Water

Charge Formulation Vessel with:

Propellant HFA 134a
Mixture of ethanol/water

Concentration of Formulation at this Process Step:

Propellant	95.45%
Ethanol	4.38%
Water	0.17%

3. Final Product Formulation

Add concentrate (from Step 1) to the mixture of propellant-ethanol-water

Concentration of Formulation at this Process Step:

Propellant	89.84%
Ethanol	10.00%
Water	0.16%
Actives	negligible
PVP	negligible
Citric acid	negligible

All publications cited in this application are incorporated herein by reference in their entirety.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

2004224367 09 Sep 2009

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A formulation comprising
water in an amount of about 0.13 to about 0.18 percent (w/w) of the product formulation,
at least one HFA as a propellant,
one or more excipients, and
active ingredients albuterol sulfate and ipratropium bromide, wherein the active ingredients of the formulation are suspended.

2. The formulation according to claim 1 wherein the amount of water is 0.13 to 0.16% w/w of the product formulation.

3. The formulation according to claim 1 wherein the HFA propellant is HFA 134a.

4. The formulation according to claim 1 wherein the excipients are ethanol, citric acid and polyvinylpyrrolidone.

5. The formulation according to claim 4 wherein the formulation is in a metered dose inhaler comprising a valve containing a metering chamber that is an area for the formulation to be dosed or dispensed to reside between actuations or dosings.

6. A metered dose inhaler comprising
a formulation according to any one of claims 1 to 5;
a valve containing a metering chamber that is an area for the formulation to be dosed or dispensed to reside between actuations or dosings.

7. A process of making a formulation according to claim 4 or 5 comprising:
preparing a concentrate by adding:
ethanol, citric acid, ipratropium bromide monohydrate, polyvinylpyrrolidone and albuterol sulfate;
preparing a propellant, ethanol and water mixture, said mixture containing:
propellant HFA 134a,
a mixture of ethanol and water;

2004224367 09 Sep 2009

adding the concentrate to the mixture of propellant-ethanol-water to provide the formulation.

8. The formulation according to claim 1, substantially as hereinbefore described with reference to any one of the examples.

9. The metered dose inhaler according to claim 6, substantially as hereinbefore described with reference to any one of the examples.

10. The process according to claim 7, substantially as hereinbefore described with reference to any one of the examples.