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(54) Title: FORMULATIONS FOR INHALATION

(57) Abstract: A pharmaceutical aerosol formulation comprising an active material coated with a polymer, in combination with a propellant, optionally with other pharmaceutically acceptable excipients.

Formulations for Inhalation

Technical field:

The present invention relates to aerosol formulations suitable for pulmonary, nasal, buccal or topical administration, which have good stability. It also relates to process for manufacturing the same.

Background and prior art

Drugs for treating respiratory disorders are frequently administered in oral aerosol formulations. One widely used method for dispensing such an aerosol drug formulation involves making a formulation of the drug in a liquefied gas known as a propellant. The drug may be dissolved or suspended in the propellant, or in a combination slurry-solution.

Chlorofluorocarbons (CFCs) have been used extensively as propellants in drug formulations that are delivered to patients via an MDI. However, recent scientific evidence suggests that CFCs damage the Earth's ozone layer. It is believed that ozone blocks harmful ultraviolet rays and that depletion of the ozone layer will result in the incidence of skin cancer. As a result, steps have been taken to reduce CFC production and usage, and recent recommendations have been made that CFC production be virtually discontinued and alternate ozone free propellants should be used.

MDI formulations containing HFA propellants do not have suspension characteristics as good as those formulations containing CFC Propellants. For example, an MDI formulation containing the beta-agonist albuterol sulfate and an anticholinergic agent, such as ipratropium bromide or tiotropium, with an HFA propellant is not a stable suspension and either quickly sediments, floats or forms an emulsion.

As a result surfactants have been used in aerosol formulations containing HFA to improve the quality of the Aerosol suspensions.

U.S. Pat. No. 5,182,097 to Byron et al. relates to aerosol formulations consisting of 1,1,1,2-tetrafluoroethane, a drug and oleic acid as a surfactant to aid in dispersing the drug in the propellant.

But using surfactants may not be feasible for all drugs because of considerable difficulties have been encountered in finding suspending agents which are soluble in hydrofluoroalkanes and capable of stabilizing medicament suspensions. Also when surfactants are used other excipients are required, in which all drugs may not be stable.

Attempts have also been made to coat drug with only surfactants or instead, but the results have not been very satisfactory. Therefore there still remains a need to provide novel ways to solve the problem of sedimentation and stability of suspension.

Object:

It is an object of the present invention is to provide a pharmaceutical aerosol formulation with good stability.

Another object of the present invention is to provide a pharmaceutical aerosol formulation that overcomes the problem of sedimentation and stability of suspension.

Still another object of the present invention is to provide a process to manufacture the pharmaceutical formulation according to the present invention.

Summary:

Thus according to a first aspect of the present invention there is provided a pharmaceutical aerosol formulation comprising the drug coated with a polymer, which is advantageously polyvinylpyrrolidone ("PVP"), in combination with a propellant, optionally with other suitable excipients.

According to a second aspect of the present invention there is provided a pharmaceutical aerosol formulation, wherein the concentration of the polymer, which is advantageously PVP, used to coat the drug is in the range of 0.00001% to 10% of the formulation. Suitably, the concentration of the polymer used to coat the drug is in the range of 0.00001% to 0.1% w/w,

typically 0.0001% to 0.001% w/w of the formulation. Preferably, the concentration of the polymer is in the range of 0.0005% to 0.0035% w/w of the formulation (which corresponds to 0.3% to 2% w/w of the active).

In an embodiment, the pharmaceutical aerosol formulation comprises the drug coated with the polymer, which is advantageously PVP, and one or more surfactants.

In another embodiment, the pharmaceutical aerosol formulation according to the present invention may further comprise either other suitable excipients or similarly coated or uncoated drug particles.

In another aspect of the present invention there is provided a process to manufacture a pharmaceutical aerosol formulation according to the present invention.

Description:

There is a need to provide novel ways to solve the problem of sedimentation and stability of suspension for aerosol formulations.

Surprisingly, we have found that certain polymers when used to coat the drug are capable of stabilizing medicament compositions and give better results than those obtained with conventional surfactants.

Accordingly certain polymers include polymers like PVP which when used to coat the drugs, yields good quality suspensions.

Further, we have found that when the concentration of the polymer, especially PVP, used for the coating is greater than or equal to 0.0005% w/w of the formulation (which corresponds to 0.3% w/w of the active), suspension quality is increased compared to concentrations below 0.0005% w/w. Also, when the concentration of the polymer is greater than 0.0035% w/w of the formulation (which corresponds to 2% w/w of the active), the formulation has a lower

FPD (fine particle dose) and also results in greater valve-sticking, compared to formulations with a concentration of polymer less than or equal to 0.0035% w/w.

Thus we have found that PVP when used (for coating) in the range of 0.0005% to 0.0035% w/w of the formulation (which corresponds to 0.3%-2% w/w of the active) gives a good suspension quality and also overcomes the problem of sedimentation.

The present invention provides a pharmaceutical aerosol formulation having good stability. More specifically, the pharmaceutical aerosol formulation comprises a pharmaceutically active agent coated with a polymer in combination with a propellant and optionally other suitable excipients. The invention is especially suitable for use with hydrofluoroalkane ("HFA") propellants.

Suitably the polymer used may be PVP (polyvinylpyrrolidone), such as PVP K17, PVP K25 or PVP K30 may be used. The PVP can be present in a range of about 0.00001% to about 10% of the formulation. Suitably, the concentration of the PVP used to coat the drug is in the range of about 0.00001% to about 0.1% w/w, typically about 0.0001% to about 0.001% w/w of the formulation. The PVP is preferably present in a range of about 0.0005% to about 0.0035% w/w of the formulation (0.3%-2% w/w of the active). More preferably, the PVP is present in the range of about 0.0005% to about 0.001% w/w of the formulation. (0.3%-0.6% w/w of the active). Still more preferably, the PVP is present in a range of about 0.0006% w/w to about 0.001% w/w of the formulation (0.35% to 0.6% w/w of the active) and most preferably about 0.0007% w/w to about 0.00095% w/w by weight of the formulation. (0.4%-0.55% w/w of the active).

The present invention provides a pharmaceutical aerosol formulation, having good stability, comprising a pharmaceutically active agent coated with PVP in combination with a propellant and optionally other suitable excipients. The invention is especially suitable for use with hydrofluoroalkane ("HFA") propellants.

In addition to the polymer, the drug may also be coated with a surfactant.

The present invention therefore also provides a pharmaceutical aerosol formulation comprising a pharmaceutically active agent coated with a polymer and surfactant in

combination with a propellant, preferably a hydrofluoroalkane ("HFA") propellant, and optionally other suitable excipients.

Suitable surfactants may comprise sorbitan trioleate, tweens, e.g., tween 20, 40, 60, 80,120, Lipids, lecithin, oleic acid, citric acid, and polyoxyethylene(4)lauryl ether (Brij 30®). Suitably the surfactant is tween 80. The surfactant can be present in a range of about 0.00001-0.01% by weight of the active.

The solvent used for dissolving the PVP or the surfactant should be such that the selected drug is either insoluble or has a suitably low solubility in the selected solvent.

In another aspect, the present invention relates to a method for coating drug particles with a polymer, especially PVP. This method is a general method for coating the drug particles.

A solution of the polymer, such as PVP, may be prepared in a solvent in which the selected drug is either practically insoluble in the solvent or has a solubility less than 0.01 to 0.1%. The concentration of the polymer solution may vary with the selected drug but is typically in the range 0.0005 to 0.0035% by weight of the formulation (0.3%-2% w/w of the active). The micronized drug powder may be added to the solution of polymer and mixed with techniques known in the art, e.g. sonicating or stirring, for about 30 min to give a homogeneous suspension. Micronized drug powder is defined as comprising particles having a mean size in the range of 1 to 5 μm. After mixing, the drug particles will be coated with a layer of the polymer solution. The coated particles may be separated from the suspension by techniques known in the art, e.g. spraying through a suitable spray drier, and dried. The powder may be collected and deaggregated to produce a free flowing powder. Optionally the powder may be subjected to conventional milling techniques to give appropriate size to the drug particles. The appropriate quantity of the coated drug and propellant may then be admixed in a suitable container to give final suspension.

In another aspect, the present invention relates to a method for coating drug particles with a polymer, especially PVP, and one or more surfactants. This method is a general method for coating the drug particles.

A solution of the polymer, such as PVP, and the surfactant may be prepared separately in a solvent in which the selected drug is either insoluble or has a suitably low solubility. The concentration of the polymer and surfactant solution varies with the selected drug. An appropriate quantity of the surfactant solution may be mixed with the solution of PVP and to this resultant solution is added the micronized drug powder and mixed with techniques known in the art, e.g. sonicating or stirring. for about 30 min to give a homogeneous suspension. Micronized drug powder is defined as comprising particles having a mean size in the range of 1 to 5 μm. After mixing, the drug particles will be coated with a layer of above polymer and surfactant solution. The coated particles may be separated from the suspension by techniques known in the art, e.g., spraying through a suitable spray drier and dried. The powder may be collected and deaggregated to produce a free flowing powder. Optionally the powder may be subjected to conventional milling techniques to give appropriate size to the drug particles. The appropriate quantity of the coated drug and propellant may then be admixed in a suitable container to give final suspension.

The coated drug particles produced by either of the two methods may further be mixed with other similarly coated or uncoated drugs and/or one or more suitable excipients selected from the group consisting of cosolvents, bulking agents, antioxidants, lubricants.

In another aspect the coated drug may be mixed with other similarly coated or uncoated drugs and optionally with surfactants.

The formulation may further comprise one or more cosolvents, such as polyethylene glycol ("PEG"), propylene glycol, isopropyl myristate or glycerol. Suitably, the cosolvent is PEG, such as PEG 200 or PEG 400. The cosolvent can be present in a range of about 0.05% to about 15% by weight of the formulation. Suitably, the cosolvent is present in a range of about 0.05% to about 1% or about 0.05% to about 0.3% by weight of the formulation.

The formulation may further comprise one or more bulking agents, preferably selected from the class of saccharides, including but not limited to monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose,

sucrose, trehalose, lactose, maltose, starches, dextran or mannitol. The bulking agent may be present in a concentration of 10-500% w/w active, more preferably in a range of 10-300% w/w active. The preferred bulking agent is lactose.

The present invention may optionally comprise antioxidants like citric acid, benzalkonium chloride.

As discussed earlier, aerosol formulations traditionally contained CFC propellants. Due to environmental concerns, HFA propellants are now preferred over CFC propellants. As will be understood by those skilled in the art, suitable HFA propellants for use in the present invention include, but are not limited to, 1,1,1,2-tetrafluoroethane (HFA-134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA-227). Optionally mixtures of two or more such halogen-substituted hydrocarbons may also be used.

The invention is particularly useful in that it allows acceptably stable dispersions to be attained using HFA Propellant as the aerosol propellant. The formulations of the invention may be prepared with HFA Propellant alone or a mixture of HFA Propellant and another miscible adjuvant having a polarity equal to or lower than the polarity of the HFA Propellant.

Suitable solid medicaments may include antiallergics, analgesics, bronchodilators, antihistamines, thereapeutic proteins and peptides, antitussives, anginal preparations, antibiotics, antiinflammatory preparations, hormones, or sulfonamides, such as, for example, a vasoconstrictive amine, an enzyme, alkaloid, or steroid, and synergistic combinations of these. Examples of medicaments which may be employed are: Isoproterenol [alpha-(isopropylaminomethyl) protocatechuyl alcohol], phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, epinephrine, ephedrine, narcotine, codeine, atropine, heparin, morphine, dihydromorphinone, ergotamine, scopolamine, adrenaline, metaproterenol, phenylephrine, phenylpropanolamine, reproterol, isoetharine, tulobuterol, orciprenaline, or(-)-4-amino-3,5 -dichloro- a-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; diuretics, e.g.amiloride methapyrilene, cyanocobalamin, terbutaline, rimiterol, salbutamol, salmeterol, formoterol, carmoterol, fenoterol, ipratropium, oxitropium, tiotropium, triamcinolone, budesonide,

fluticasone, tipredane, mometasone, ciclesonide, flunisolide, colchicine, pirbuterol, beclomethasone, orciprenaline, fentanyl, and diamorphine, diltiazem. Others are antibiotics, such as neomycin, streptomycin, penicillin, procaine penicillin, sulphonamides, pentamidine, tetracycline, chlorotetracycline and hydroxytetracycline; adrenocorticotropic hormone and adrenocortical hormones, such as cortisone, hydrocortisone, hydrocortisone acetate and prednisolone; insulin, antiallergy compounds such as cromolyn sodium, ketotifen ornedocromil etc. xanthines e.g. aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, e.g. insulin or glucagons.

The therapeutic agents mentioned above as well as the drugs throughout the specification are used in a broad sense to include not only various therapeutic agents and drugs per se but also their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs or pharmaceutically acceptable prodrugs thereof.

The following salts of the drugs mentioned above may be used; acetate, benzenesulphonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, fluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulphate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, and triethiodide.

Cationic salts may also be used. Suitable cationic salts include the alkali metals, e.g. sodium and potassium, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, e.g. glycine, ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 1-amino-2-propanol-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2 isopropylaminoethanol.

Preferred drugs for use with the invention are betamimetics and anticholinergics. The terms "betamimetics" or "anticholinergic agent" are used in a broad sense to include not only the betamimetics or anticholinergic agent per se but also their pharmaceutically acceptable salts, pharmaceutically acceptable solvates and pharmaceutically acceptable hydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable derivatives, pharmaceutically acceptable polymorphs or pharmaceutically acceptable prodrugs thereof

Betamimetic agents useful in the formulations of the present invention include, but are not limited to, albuterol, formoterol, levalbuterol, carmoterol, pirbuterol and salmeterol. The international name for albuterol is salbutamol. Suitable pharmaceutically acceptable salts of the betamimetics include, but are not limited to the hydrochloride, sulfate, maleate, tartrate, and citrate salts. Suitably, the betamimetic is albuterol or albuterol sulfate.

Anticholinergic agents useful in the formulations of the present invention include, but are not limited to, oxitropium, ipratropium and tiotropium. Suitable pharmaceutically acceptable salts of the anticholinergic agents include, but are not limited to, the halide salts such as bromide, chloride and iodide. Suitably, the anticholinergic agent is ipratropium or ipratropium bromide or ipratropium bromide monohydrate.

Particularly suitable salts are disclosed in the examples. It will be understood that the specific therapeutic agents mentioned in the examples may be used in the invention, not necessarily in the combinations mentioned. It will also be appreciated that the specific therapeutic agents mentioned in the examples may be used in the amounts specified with other therapeutic agents.

The invention also provides, in another aspect, a metered dose inhaler (MDI) comprising (i) a housing containing a pharmaceutical composition as described above; and (ii) means enabling the application of the composition from within the housing by oral administration directly to the lungs.

It has been observed that some aerosol drugs tend to adhere to the inner surfaces, i.e., walls of the cans and valves, of the MDI. This can lead to the patient getting significantly less than

the prescribed amount of the active agent upon each activation of the MDI. Coating the inner surface of the container with a suitable polymer can reduce this adhesion problem. Suitable coatings include, but are not limited to, fluorocarbon copolymers such as FEP-PES (fluorinated ethylene propylene and polyethersulphone) and PFA-PES (perfluoroalkoxyalkane and polyethersulphone), epoxy and ethylene.

Also, during storage, moisture can enter the MDI mainly through the crimped area of the valve and through the stem by diffusion. To reduce the amount of moisture entering the MDI, the metering valve is suitably comprised of a butyl elastomer.

Each filled canister is conveniently fitted into a suitable actuator for administration of the medicament into the lungs of a patient. . Metered dose inhalers are designed to deliver a fixed unit dosage of medicament per actuation or "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. The formulation of the present invention may be administered one, two, three or four times per day with one or more activations, e.g. two, three or four activations, of the metering valve per administration to treat broncho-constriction, asthma and related disorders thereof.

The following examples are for the purpose of illustration of the invention only and are not intended in any way to limit the scope of the present invention.

Manufacture of coated drug:

Example 1

0.5% w/w (of active) of PVP K17 is dissolved in about 250 ml of dried acetone. To this solution salbutamol sulphate is added and sonicated for about 30 min. This is then further spray dried to obtain coated salbutamol.

Example 2

50 mg of Tween 80 is added in 100ml of alcohol and sonicated. 0.5% w/w (of active) of PVP K17 is dissolved in about 250 ml of dried acetone and sonicated. To this solution is added about 0.02 ml of above prepared tween 80 solution. To this solution salbutamol sulphate is added and sonicated for about 30 min. This is then further spray dried to obtain coated salbutamol.

In all formulations exemplified below, the percentage of polymer is expressed as w/w of active and the percentage of surfactant is also expressed as w/w of active.

Formulation 1

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	28.8 mg
PEG 400	16.8mg
HFA-227	Q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 2

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
levalbuterol Sulfate coated with 0.5%PVP K17	14.4 mg
PEG 400	16.8mg
HFA-227	Q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 3

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg

levalbuterol Sulfate coated with 0.5%PVP K17	14.4 mg
PEG 400	50.4mg
HFA-227	Q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 4

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	28.8 mg
PEG 400	50.4 mg
HFA-227	Q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 5

	Qty/can
levalbuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	28.8 mg
PEG 400	50.4 mg
HFA-227	Q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 6

	Qty/can
tiotropium Bromide	1.8 mg
formoterol fumarate coated with 0.5%PVP K17 and 0.0002% tween 80	0.96 mg
PEG 400	16.8mg

HFA-227	q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 7

	Qty/can
tiotropium Bromide	1.8 mg
formoterol fumarate coated with 0.5%PVP K17	0.96 mg
PEG 200	50.4mg
HFA-227	q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 8

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
levalbuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	14.4 mg
PEG 400	50.4 mg
HFA-227	Q.s

(a) The active ingredients were added to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 9

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17	14.4 mg
HFA-227	Q.s

a) The active ingredients were added to the canister.

b) the canister was crimped with the metered valve

c) the canister was charged with HFA227 .

Formulation 10

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17	14.4 mg
lactose	1.8 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the propellant.

Formulation 11

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17	14.4 mg
lactose	1.8 mg
PEG 400	16.8 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 12

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17	14.4 mg
PEG 400	50.4 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 13

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	14.4 mg
lactose	1.8 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the propellant.

Formulation 14

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	14.4 mg
lactose	1.8 mg
PEG 400	16.8 mg
HFA-227	q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 15

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	14.4 mg
PEG 400	16.8 mg
HFA-227	q.s

(a) The active ingredients to the canister.

(b) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 16

	Qty/can
Levalbuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	14.4 mg
HFA-227	Q.s

a) The active ingredients were added to the canister.

b) the canister was crimped with the metered valve

c) The canister was charged with HFA227.

Formulation 17

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17	28.8 mg
HFA-227	Q.s

d) The active ingredients were added to the canister.

e) the canister was crimped with the metered valve

f) the canister was charged with HFA227 .

Formulation 18

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17	28.8 mg
lactose	4.23 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the propellant.

Formulation 19

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17	28.8 mg
lactose	4.23 mg

PEG 400	16.8 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 20

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17	28.8 mg
lactose	4.23 mg
PEG 400	50.4 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 21

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	28.8 mg
lactose	4.23 mg
HFA-227	Q.s

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the propellant.

Formulation 22

	Qty/can

Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	28.8 mg
lactose	4.23 mg
PEG 400	16.8 mg
HFA-227	20.2 gm

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Formulation 23

	Qty/can
Ipratropium Bromide monohydrate	5.04 mg
Albuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80	28.8 mg
lactose	4.23 mg
PEG 400	16.8 mg
HFA-227	20.2 gm

(a) The active ingredients to the canister.

(b) Lactose was added to (a)

(c) The canister was crimped with the metered valve and was charged with the solution of propellant and PEG.

Table 1. Effect of combinations of drug coated with Surface modifying or PVP and surfactant on the suspension characteristics and Suspension quality of ipratropium bromide and albuterol sulfate.

	Active Ingredients	Cosolvent	Bulking agent	Propellant	Suspension characteristics and suspension quality.
1	Ipratropium (5.04 mg) Albuterol sulfate (28.8 mg)	--	--	HFA Propellant (P134a or P227)	Particles remain in homogeneous suspension for less than 5 seconds.
2	Ipratropium (5.04 mg) Albuterol sulfate coated with only surfactant (28.8 mg)		--	HFA Propellant (P134a or P227)	Particles remain in homogeneous suspension for about 20-25 seconds.
3	Ipratropium (5.04 mg) Albuterol Sulfate coated with 0.5%PVP K17 (28.8 mg)	--	--	HFA Propellant (P134a or P227)	Particles remain in homogeneous suspension for about 35 seconds to 1 minute.
4	Ipratropium (5.04 mg) Albuterol Sulfate coated with 0.5%PVP K17 (28.8 mg)	PEG 200/400 (0.1% and 0.3% of total formulation)	--	HFA Propellant (P134a or P227)	Particles remain in homogeneous suspension for about 35 seconds to 1 minute.
5	Ipratropium (5.04 mg) Albuterol Sulfate coated with 0.5%PVP K17 (28.8 mg)	PEG200/ 400 (0.1% and 0.3% of total formulation)	12.5% of total active	HFA Propellant (P134a or P227)	Particles remain in homogeneous suspension for about 35 seconds to 1 minute.
6	Ipratropium (5.04 mg) Albuterol Sulfate coated with 0.5%PVP K17 and 0.0002%	--	12.5% of total active	HFA Propellant (P134a or P227)	Particles remain in homogeneous suspension for about 35 seconds to 1

	tween 80 (28.8 mg)				minute.
7	Ipratropium (5.04 mg) Albuterol Sulfate coated with 0.5%PVP K17 and 0.0002% tween 80 (28.8 mg)	PEG200/ 400 (0.1% and 0.3% of total formulation)	12.5% of total active	HFA Propellant (P134a or P227)	Particles remain in homogeneous suspension for about 35 seconds to 1 minute.

Table 2: Effect of combinations of drug coated with varying concentrations of PVP on the Suspension quality , FPD and valve sticking of ipratropium bromide and albuterol sulfate HFA inhaler and also.

Sr. No	Concentration of PVP used for coating (% w/w of the drug)	Suspension quality	Fine particle dose (FPD) (%)		Valve sticking
			Ipratropium	Albuterol	
1.	0.1	Poor	----*	----*	no
2.	0.2	Poor	----*	----*	no
3.	0.4	Good	36.64	40.92	no
4.	0.5	Good	33.33	40.84	no
5.	0.7	Good	35.83	40.62	no
6.	1	Good	46.89	46.45	slight
7.	5	Good	18.33	21.97	heavy
8.	10	Good	33.94	7.43	heavy
9.	20	Good	25.61	6.12	heavy

*not evaluated due to unacceptable suspension quality.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having" and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a propellant" includes a single propellant as well as two or more different propellants, reference to a "cosolvent" refers to a single cosolvent or to combinations of two or more cosolvents, and the like.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

Claims

1. A pharmaceutical aerosol formulation comprising an active material coated with a polymer, in combination with a propellant, optionally with other pharmaceutically acceptable excipients.

2. A formulation according to claim 1, wherein the polymer is a polyvinylpyrrolidone ("PVP").

3. A formulation according to claim 2, wherein the PVP is PVP K17, PVP K25 or PVP K30.

4. A formulation according to claim 1, 2 or 3, wherein the concentration of the polymer, used to coat the active material is in the range of 0.00001% to 1 % w/w of the formulation.

5. A formulation according to claim 1, 2 or 3, wherein the concentration of the polymer, used to coat the active material is in the range of 0.0001% to about 0.01% w/w of the formulation.

6. A formulation according to claim 1, 2 or 3, wherein the concentration of the polymer, used to coat the active material is in the range of 0.0005% w/w to about 0.0035% w/w of the formulation.

7. A formulation according to any preceding claim further comprising a surfactant.

8. A formulation according to claim 7, wherein the surfactants comprises sorbitan trioleate, a tweens, a lipid, lecithin, oleic acid, citric acid, or polyoxyethylene(4)lauryl ether.

9. A formulation according to claim 8, wherein the surfactant is tween 80.

10. A formulation according to claim 8 or 9, wherein the surfactant is present in a range from 0.00001 to 0.01% w/w of the active.

11. A formulation according to any preceding claim, further comprising a cosolvent.

12. A formulation according to claim 11, wherein the cosolvent is a polyethylene glycol, a propylene glycol, isopropyl myristrate or glycerol.

13. A formulation according to claim 11 or 12, wherein the cosolvent is present in a range from 0.05% to 15% w/w of the formulation.

14. A formulation according to any preceding claim, further comprising a bulking agent.

15. A formulation according to claim 14, wherein the bulking agent is a saccharide.

16. A formulation according to claim 14 or 15, wherein the bulking agent is lactose.

17. A formulation according to claim 14, 15 or 16, wherein the bulking agent is present in a concentration from 10% to 500% w/w of the active.

18. A formulation according to any preceding claim, wherein the propellant is a hydrofluoroalkane ("HFA") propellants.

19. A formulation according to claim 18, wherein the HFA propellant is 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227), or a mixture thereof.

20. A formulation according to any preceding claim, wherein the active material is selected from: Isoproterenol [alpha-(isopropylaminomethyl) protocatechuyl alcohol], phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, epinephrine, ephedrine, narcotine, codeine, atropine, heparin, morphine, dihydromorphinone, ergotamine, scopolamine, adrenaline, metaproterenol, phenylephrine, phenylpropanolamine, reproterol,

isoetharine, tulobuterol, orciprenaline, (-)-4-amino-3,5 -dichloro- a-[[[6-[2-(2-pyridinyl)ethoxy]hexyl]amino]methyl]benzenemethanol; amiloride methapyrilene, cyanocobalamin, terbutaline, rimiterol, salbutamol, salmeterol, formoterol, carmoterol, fenoterol, ipratropium, oxitropium, tiotropium, triamcinolone, budesonide, fluticasone, tipredane, mometasone, ciclesonide, flunisolide, colchicine, pirbuterol, beclomethasone, orciprenaline, fentanyl, diamorphine, diltiazem, neomycin, streptomycin, penicillin, procaine penicillin, sulphonamides, pentamidine, tetracycline, chlorotetracycline, hydroxytetracycline, cortisone, hydrocortisone, hydrocortisone acetate, prednisolone, insulin, cromolyn sodium, ketotifen, ornedocromil, aminophylline, choline theophyllinate, lysine theophyllinate, theophylline or a pharmaceutically acceptable salt thereof.

21. A formulation according to any one of claims 1 to 19, wherein the active material is an betamimetic and/or an anticholinergic.

22. A formulation according to claim 21, wherein the betamimetic is albuterol, formoterol, levalbuterol, carmoterol, pirbuterol and salmeterol or a pharmaceutically acceptable salt thereof.

23. A formulation according to claim 22, wherein the betaimimetic is albuterol or albuterol sulfate.

24. A formulation according to claim 21, 22 or 23, wherein the anticholinergic is oxitropium, ipratropium and tiotropium.

25. A formulation according to claim 24, wherein the anticholinergic is ipratropium, ipratropium bromide or ipratropium bromide monohydrate.

26. A method of preparing a formulation according to any preceding claim, comprising preparing a solution of the polymer, optionally with the surfactant, in a solvent in which the active material is either insoluble or has a low solubility; adding a micronized drug powder to the solution of polymer and mixing the drug powder and the solution to coat the drug

particles with a layer of the polymer solution; and separating the coated particles from the suspension; and mixing the coated drug with the propellant.

27. The use of a polymer coating to stabilise a pharmaceutical aerosol formulation comprising an active material in combination with a propellant.

28. The use according to claim 27, wherein the polymer is a PVP.

29. The use according to claim 27 or 28, wherein the concentration of the polymer, used to coat the active material is in the range of 0.0005% to 0.0035% w/w of the formulation.

30. The use according to claim 27, 28 o 29, wherein the formulation further comprises a surfactant.

31. The use according to claim 27, 28, 29 or 30, wherein the propellant is an HFA propellant.

32. A nasal spray dispenser comprising (i) a housing containing a pharmaceutical composition according to any one of claims 1 to 26; and (ii) means enabling the application of the composition from within the housing to the nasal mucosa.