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(54) Title: STABILIZED MEDICINAL AEROSOL SOLUTION FORMULATIONS

(57) Abstract

Stabilized medicinal aerosol solution formulations comprising medicaments that tend to degrade by interaction with solvents or water, an HFC propellant, a cosolvent and an acid are described. Further, specific medicinal aerosol solution formulations comprising ipratropium bromide, ethyl alcohol, 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, and either a strong inorganic acid or weak organic acid are described.

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STABILIZED MEDICINAL AEROSOL SOLUTION FORMULATIONS

This invention relates to stable pharmaceutical solution formulations suitable for aerosol administration. More particularly, this invention relates to stable pharmaceutical solution formulations suitable for aerosol administration wherein either a strong inorganic acid or a weak organic acid is added to the aerosol solution formulation which contains a medicament in solution with an environmentally safe hydrofluorocarbon (HFC) as a propellant, together with an organic compound as a cosolvent. The acid provides stability against degradation or decomposition of the medicament resulting largely from interaction of the medicament with the cosolvent and/or water present in the solution formulation.

BACKGROUND OF THE INVENTION

The administration of aerosol formulations of medicaments by means of pressurized, metered-dose inhalers (MDIs) is used widely in therapy, such as in the treatment of obstructive airway diseases and asthma. Compared with oral administration, inhalation provides more rapid onset of action while minimizing systemic side effects. Aerosol formulations can be administered by inhalation through the mouth or topically by application to the nasal mucosa.

Formulations for aerosol administration via MDIs can be solutions or suspensions. Solution formulations offer the advantage of being homogeneous in nature with the medicament and excipients completely dissolved in the propellant vehicle. Solution formulations also obviate physical stability problems associated with suspension formulations and thus assure more consistent uniform dosage administration while also eliminating the need for surfactants.

The administration of aerosol solution formulations via MDIs is dependent upon the propulsive force of the propellant system used in its manufacture.

Traditionally, the propellant comprised a mixture of chlorofluorocarbons (CFCs) to provide the desired solubility, vapor pressure, and stability of the formulation. However, since it has been established in recent years that CFCs are environmentally harmful because they contribute to the depletion of the Earth's ozone layer, it is desirable to substitute environmentally safe hydrofluorocarbon (HFC) propellants or other non-chlorinated propellants for environmentally harmful CFC propellants in aerosol inhalation formulations. For example, U.S. Patent No. 4,174,295 discloses the use of propellant systems consisting of combinations of HFCs, which may also contain a saturated hydrocarbon component, suitable for application in the fields of home products such as hair lacquers, anti-perspiration products, perfumes, deodorants, paints, insecticides and the like.

It is known in the art that certain HFCs have properties suitable for use as propellants for the aerosol administration of medicaments. For example, published European Patent Application No. 0 372 777 (EPO89312270.5) describes the use of 1,1,1,2-tetrafluoroethane (HFC-134(a)) in combination with at least one "adjuvant" (a compound having a higher polarity than the HFC-134(a)) and a surface active agent to prepare suspension and solution formulations of medicaments suitable for administration by the aerosol route. Also, PCT Published Application No. W091/11496 (PCT/EP91/00178) discloses the use of 1,1,1,2,3,3,3-heptafluoropropane (HFC-227), optionally mixed with other propellant components, for use in preparing suspension aerosol formulations of medicaments.

BRIEF DESCRIPTION OF THE INVENTION

It has now been found that the use of propellant systems containing an HFC and a cosolvent in aerosol solution formulations presents a chemical stability problem that has not been previously recognized or resolved in the prior art. This is because in such HFC propellant/cosolvent

systems, the medicament may interact with the cosolvent and/or water present in the system to produce decomposition or degradation products. It has now further been found that the addition of an acid, either a strong inorganic acid or a weak organic acid, to the HFC propellant/cosolvent system provides the requisite chemical stability to the medicament.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 is a graph that summarizes invention results.

DESCRIPTION OF THE PREFERRED EMOBDIMENTS

The term "aerosol suspension formulation" means a pharmaceutical formulation of a medicament suitable for aerosol administration wherein the medicament and excipients are present in the form of a finely divided suspension.

The term "aerosol solution formulation" means a pharmaceutical formulation of a medicament suitable for aerosol administration wherein the medicament and excipients are completely dissolved.

The term "stabilized aerosol solution formulation" means an aerosol solution formulation which exhibits substantial chemical stability over time.

Ipratropium bromide is an anticholinergic bronchodilator marketed under the trademark "ATROVENT." This medicament is administered as an aerosol suspension formulation which contains a mixture of CFCs (dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane) as the propellant, and soya lecithin.

Studies have demonstrated that stable aerosol solution formulations of ipratropium bromide can be obtained by dissolving ipratropium bromide in a homogeneous system comprising HFC-134(a), ethanol, and a strong inorganic acid or a weak organic acid. The particular type and amount of acid added to the system will define the level of acidity which is critical in obtaining a stable solution formulation.

Thus, the present invention provides stabilized aerosol solution formulations comprising a medicament, an HFC propellant, a cosolvent, and a strong inorganic acid or weak organic acid. A small amount of water (up to about 5% by weight) may also be present in the propellant/cosolvent system.

Suitable HFC propellants are those which, when mixed with the cosolvent(s), form a homogeneous propellant system in which a therapeutically effective amount of the medicament can be dissolved. The HFC propellant must be toxicologically safe and must have a vapor pressure which is suitable to enable the medicament to be administered via a pressurized MDI. Additionally, the HFC propellant must be compatible with the components of the MDI device (such as containers, valves, and sealing gaskets, etc.) which is employed to administer the medicament. Preferred HFC propellants are 1,1,1,2-tetrafluoroethane (HFC-134(a)) and 1,1,1,2,3,3,3,-heptafluoropropane (HFC-227). HFC-134(a) is particularly preferred. Other examples of HFC propellants are HFC-32 (difluoromethane), HFC-143(a) (1,1,1-trifluoroethane), HFC-134 (1,1,2,2-tetrafluoroethane), and HFC-152a (1,1-difluoroethane).

It will be apparent to those skilled in the art that non-halogenated hydrocarbon propellants may be used in place of the HFC propellants in the present invention. Examples of non-halogenated hydrocarbons are saturated hydrocarbons, including propane, n-butane, and isobutane, and ethers, including diethyl ether.

It will also be apparent to those skilled in the art that, although the use of a single HFC propellant is preferred, a mixture of two or more HFC propellants, or a mixture of at least one HFC propellant and one or more non-CFC propellants, may be employed in the aerosol solution formulation of the present invention.

A substantially non-aqueous HFC propellant/cosolvent system is preferred. Water may be

present in small amounts as an impurity in the HFC propellant/cosolvent system, or, if desired, small amounts of water may be added (up to about 5% by weight) to the HFC/propellant system, for example, to aid in manufacturing.

If desired, pharmaceutically acceptable excipients can be included in the aerosol solution formulations of the present invention. For example, a soluble surface active agent can be added in order to improve the performance of valve systems employed in the MDI devices used for the aerosol administration of the formulations. Examples of preferred surface active agents are oleic acid, sorbitan trioleate, lecithin, and isopropylmyristate. Other suitable lubricants are well known in the art (see, for example, Published European Patent Application No. 0372777 (EPO 893122705)). Other excipients are: (a) antioxidants, for example ascorbic acid and tocopherol; (b) taste masking agents, for example, menthol, sweeteners, and artificial or natural flavors; and (c) pressure modifying agents, for example, n-pentane, iso-pentane, neo-pentane, and n-hexane.

The medicaments used in the present invention may be any substance which is suitable for aerosol administration from an MDI or similar device. The medicament must be soluble in the HFC propellant/cosolvent system and, characteristically exhibit significant degradation or decomposition in the HFC propellant/cosolvent system. The degradation or decomposition of the medicament must be acid sensitive in that the rate of degradation or decomposition can be effectively reduced by the addition of acid.

The decomposition and the degradation of the medicament may occur by various chemical mechanisms, the most significant being interaction of the medicament with the cosolvent or with the water present in the system to form hydrolysis, esterification, and/or ether products.

The amount of medicament employed in the aerosol solution formulations of the present invention is that which

is effective in producing the intended therapeutic effect, i.e., an amount such that one or more metered volumes of the formulation will deliver an effective amount of the medicament. It will be apparent to those skilled in the art that the potency of the particular medicament employed in the aerosol solution formulation will determine the amount of medicament in the formulation. In general, the medicament is present in an amount from about 0.001 to 10 percent by weight of the total weight of the formulation. An amount of from about 0.01 to 1.0 percent by weight of the total weight of the formulation is preferred.

Bronchodilators (in particular anticholinergics and sympathomimetics) are the preferred class of medicaments for use in the aerosol solution formulations of the present invention. Those skilled in the art will recognize that other classes of medicaments can in general be used. Examples of such classes are: antihistamines, antiallergics, antiinflammatories, PAF-antagonists, antitussives, antibiotics, mast cell stabilizers, mucolytics, antineoplastics, antiinfectives, vaccines, anesthetics, diagnostic agents, analgesics, antianginals, leukotriene antagonists, and 5-lipoxygenase antagonists. The medicaments can also be various types of organic molecules, including, but not limited to, hormones, enzymes, proteins, peptides, steroids, alkaloids, or combinations thereof.

The most preferred example of the medicaments for use in the aerosol solution formulations of the present invention is ipratropium bromide. Other preferred examples are oxitropium bromide (BA253), albuterol, metaprateren0l, tiotropium bromide (BA-679), and fenoterol.

Other examples of medicaments are:

Sympathomimetic Bronchodilators:

(a) alpha-adrenergic agonists: ephedrine, epinephrine. norfenefrine, phenylephrine, and phenylpropanolamine.

(b) beta-adrenergic agonists: bambuterol, bitoterol,

carbuterol, clenbuterol, ephedrine, formoterol, hexoprenaline, isoproterenol, mabuterol, pirbuterol, reproterol, rimiterol, terbutaline, and tulobuterol.

Anticholinergic Bronchodilators: telenzepine, troventol, and flubron.

Alkaloids: atropine, scopolamine, and bromocriptine.

The medicaments used in the present invention may be in the form of either the free base or a pharmaceutically acceptable, non-toxic, salt thereof. Suitable salts are well known in the pharmaceutical and medicinal arts. The selection of a particular salt will depend upon the chemical nature of the base and the chemical stability and solubility of the salt in the formulation. Examples of salts that may be employed are: acetate, benezenesulphonate, benzoate, bicarbonate, bitartrate, bromide, calcium edentate, camsylate, esylate, fumarate, fluceptate, gluconate, glutamate, glycolarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methysulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, and triethiodide. Cationic salts may also be used. Examples of cationic salts include the alkali metals, e.g. sodium and potassium, and ammonium salts and salts of amines known 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(3, 4-dihydroxyphenyl)-2-isopropylaminoethanol.

The chemical nature of the medicament defines the nature of the cosolvent, which may be any one of a number of organic solvents that are toxicologically safe and amenable to MDI solution formulations. By "cosolvent" is meant any

solvent which is miscible in the formulation in the amount desired and which, when added provides a formulation in which the medicament can be dissolved in therapeutically effective amounts. Examples of cosolvents that contain hydroxyl functions (or other functions) capable of interacting with the medicament(s) in the formulation are: alcohols, for example, ethyl alcohol and isopropyl alcohol; glycols, for example, propylene glycol, polyethylene glycols, polypropylene glycols, glycol ethers, and block copolymers of oxyethylene and oxypropylene; and other substances, for example, glycerol, polyoxyethylene alcohols, and polyoxtethylene fatty acid esters.

Examples of cosolvents that may be inert to interaction with the medicament(s) are hydrocarbons, for example, n-propane, n-butane, isobutane, n-pentane, iso-pentane, neo-pentane, and n-bexane; and ethers, for example, diethyl ether.

A preferred cosolvent according to this invention is ethyl alcohol (ethanol).

The purpose of the cosolvent is to increase the solubility of the medicament and the excipients in the formulation. Thus, the amount of cosolvent present in the formulation defines the maximum amount of medicament and excipients that can be dissolved at a particular temperature.

The selection of the acid in the aerosol solution formulations of this invention depends on the medicament used and the acid concentration needed to effect an acceptable rate of degradation of the medicament. The acid may be any strong inorganic or mineral acid, for example, hydrochloric acid, sulfuric acid, nitric acid, or phosphoric acid, or the like. The acid may also be selected from the group of acids known to those skilled in the art as organic acids, which are considered to be weak acids relative to the strong inorganic acids. Representative of this group and preferred in this invention are ascorbic acid and citric

acid, although other organic acids may also be suitable.

According to this invention an aerosol solution formulation comprising a particular medicament may be formulated using acids selected from either of the above groups.

The methods used to introduce the acid into the formulation may include: (1) the direct addition of a strong inorganic acid or weak organic acid; (2) the addition of the medicament as an acidic salt thereby generating the correct acidity level in situ, and (3) combinations of (1) and (2). Appropriate salts for introducing the medicament into the formulation will be apparent to those skilled in the art.

Laboratory experiments have demonstrated that aerosol solution formulations of ipratropium bromide in HFC-134(a) and about 35% ethanol exhibit significant decomposition of the ipratropium bromide when stored at 50°C. The decomposition can be attributed to oxidation, chemical dehydration, hydrolysis and esterification. However, tropic acid ethyl ester is the chief degradation product. This ester can be formed by the direct reaction of ethanol with ipratropium bromide or by hydrolysis of ipratropium bromide followed by esterification of tropic acid with ethanol. Addition of 1% water reduced the decomposition due to dehydration. Carrying out the reaction under nitrogen atmosphere reduced the oxidation products.

In aqueous solution the rate of hydrolysis and esterification is typically pH dependent. In aqueous solution, the degradation of ipratropium bromide exhibits a pH-rate minimum at pH 3.5. This corresponds to a hydrogen ion concentration of 3.2×10^{-4} molar (M). Although the concept of pH is poorly defined in non-aqueous systems, formulation evaluation studies were conducted using this concentration of hydrochloric acid in the HFC-134(a)/ethanol system containing ipratropium bromide. Samples stored at 50°C for five and one-half months exhibited less than 5.5%

loss of ipratropium bromide. A summary of these results is illustrated in Figure 1.

A range of chemical compositions is given in Table 1 for aerosol solution formulations containing ipratropium bromide, HFC-134(a), and a strong inorganic acid, such as hydrochloric, nitric phosphoric, or sulfuric acid. The amount of alcohol present in the formulation defines the maximum amount of ipratropium bromide that can be dissolved at a particular temperature. The range of ipratropium bromide concentrations given in Table 1 is based on the maximum, amount that can be safely dissolved without precipitation at room temperature for a given alcohol concentration. Acid content is given in units of normality which defines a pH range equivalent to 2.0 - 4.7 in an aqueous system.

TABLE 1

Ipratropium Bromide Aerosol Solution Formulations:

Range Of Chemical Compositions For A Strong Acid Formulation

Component	Content per MDI Container
Ipratropium Bromide as the Monohydrate	0.001 - 2.5% wght./wght.
Dehydrated (Absolute) Ethanol, USP	1.0 - 50.0% wght./wght.
1,1,1,2-Tetrafluoroethane, (HFC-134(a)) (Dupont Pharmaceutical Toxicity Grade)	50.0 - 99.0% wght./wght.
Strong Inorganic Acid, USP/NF (Hydrochloric Acid)	0.01 - 0.00002 Normal
Water (Purified), USP	0.0 - 5.0% wght./wght.

A range of chemical compositions is given in Table 2 for aerosol solution formulations containing ipratropium bromide, HFC-134(a), and the weak organic acid, ascorbic acid. The range of ascorbic acid concentration presented in Table 2 was based on its acid dissociation constant(s), pKa(s), and the optimal pH range for a stable ipratropium bromide formulation (2.0-4.7) in an aqueous system. For ascorbic acid, 0.0045-275 mg/ml would be required in the formulation to correspond to an aqueous pH range of 2.0-4.7. However, solubility limitations must also be taken into consideration given the fact that ascorbic acid is only soluble to about 20 mg/ml in absolute ethanol and is expected to have a lesser solubility in an absolute ethanol/HFC-134a system. Optimally, about 0.30 mg/ml of ascorbic acid is expected to be required in such a formulation corresponding to a pH-degradation rate minimum of pH 3.5 for ipratropium bromide in an aqueous system. The information contained in Table 2 is presented for ascorbic acid and gives a range of ethanol content that is based on the expected room temperature solubility of ipratropium

bromide (as the monohydrate), not taking into account the solubility limit of ascorbic acid in such a HFC-134a system. Optimally, about 0.30 mg/ml of ascorbic acid is expected to be required in such a formulation corresponding to a pH-degradation rate minimum of pH 3.5 for ipratropium bromide in an aqueous system.

The range of concentration presented in Table 2 for ascorbic acid will differ for another weak organic acid depending on its acid dissociation constant(s). For example about 0.0039-27.7 mg/ml of citric acid would be required in the formulation corresponding to an optimal aqueous pH range of 2.0-4.7 for ipratropium bromide, not taking into account solubility limitations for citric acid in an ethyl alcohol/HFC-134a system.

The range of acid concentration required to effect an acceptable rate of decomposition for medicaments in primarily non-aqueous solution aerosol formulations will depend primarily on the chemical composition of the formulation (such as choice of cosolvent(s) and the chemical nature of the medicaments(s) present. This range is expected to be about 0.10 - 0.0000001 normal for strong inorganic acids corresponding to an aqueous pH range of about 1.0-7.0 and must be calculated for weak organic acids depending on their pKa values.

TABLE 2

Ipratropium Bromide Aerosol Solution MDI Formulations:

Range Of Chemical Composition For A Weak Acid Formulation

Component	Contents per Container
Ipratropium Bromide as the Monohydrate	0.001 - 2.5% wght./wght.
Dehydrated (Absolute) Ethanol, USP	1.0 - 50.0% wght./wght.
1,1,1,2-Tetrafluoroethane, HFC-134(a)) (Dupont Pharmaceutical Toxicity Grade)	50.0 - 99.0% wght./wght.
Ascorbic Acid, USP	0.00015 - 275 mg/ml
Water (Purified), USP	0.0 - 5.0% wght./wght.

The amount of drug that can be delivered through the valve of an aerosol solution formulation will depend on the active ingredient concentration (mg/ml) in the formulation and the metering volume (ul) of the valve. Commonly used valve sizes are 25, 50, 63 and 100 ul.

Metered dose inhalers containing aerosol solution formulations of medicaments can be manufactured using a number of conventional processing methods. One method, which is useful in the laboratory for the manufacture of small laboratory scale lots, is Dual Stage Pressure Fill. This method is shown in Tables 3 and 4 for two specific ipratropium bromide solution formulations using a 50-ul valve. Two methods for large scale manufacture are Single-Stage Cold Fill and Single-Stage Pressure Fill.

TABLE 3

Ipratropium Bromide Inhalation Aerosol, 0.021 mg Drug Delivered Through The Valve, 12 ml

I. Composition

Component	Contents per Container
Ipratropium Bromide Monohydrate	0.00505
Dehydrated (Absolute) Alcohol, USP	2.02500
1,1,1,2-Tetrafluoroethane, HFC-134a) (Dupont Pharmaceutical Toxicity Grade)	11.40209
Nitric Acid, USP/NF	0.00036
Water (Purified), USP	0.06750
	TOTAL: 13.50000

I. Device Components

Suitable Aerosol Container
50 ul Aerosol Metering Valve

III. Brief Description of Processing Method

An active ingredient concentrate is prepared by dissolving the ipratropium bromide, as the monohydrate, nitric acid, and water in ethyl alcohol. The concentrate is added to an appropriate filling apparatus. The active ingredient concentrate is dispensed into aerosol containers. The headspace of the containers is purged with nitrogen or HFC-134a vapor (purging ingredients should not contain more than 1 ppm oxygen) and is sealed with valves. The HFC-134a propellant is then pressure-filled into the sealed containers.

TABLE 4

Ipratropium Bromide Inhalation Aerosol, 0.021 mg Drug Delivered Through The Valve, 12 ml

I. Composition

Component	Stated Contents Per Container (g)
Ipratropium Bromide Monohydrate	0.00505
Dehydrated (Absolute) Ethyl Alcohol, USP	2.02500
1,1,1,2-Tetrafluoroethane (HFC-134A), (Dupont Pharmaceutical Toxicity Grade)	11.26745
Ascorbic Acid, USP	0.13500
Water (Purified), USP	0.06750
	TOTAL13.50000

II. Device Components:

Suitable Aerosol Container
50 ul Aerosol Metering Valve

III. Brief Description Of Processing Method

An active ingredient concentrate is prepared by dissolving the ipratropium bromide, as the monohydrate, ascorbic acid and water in ethyl alcohol. The concentrate is added to an appropriate filling apparatus. The active ingredient concentrate is dispensed into aerosol containers, the headspace of the containers is purged with Nitrogen or HFC-134a vapor (purging ingredients should not contain more than 1 ppm oxygen) and is sealed with valves. The HFC-134a propellant is then pressure filed into the sealed containers.

We Claim:

1. An aerosol solution formulation comprising a medicament, an HFC propellant, an organic cosolvent, and either a strong inorganic acid or weak organic acid.

2. An aerosol solution formulation according to Claim 1 wherein the HFC propellant is 1,1,1,2-tetrafluoroethane.

3. An aerosol solution formulation according to Claim 2 wherein the organic cosolvent is ethyl alcohol.

4. An aerosol solution formulation according to Claim 3 wherein the ethyl alcohol is in the range of about 1.0 to 50.0% wght./wght. of the formulation.

5. An aerosol solution formulation according to Claim 3 wherein the strong inorganic acid is selected from the group consisting of sulfuric acid, hydrochloric acid, nitric acid, and phosphoric acid.

6. An aerosol solution formulation according to Claim 5 wherein the strong inorganic acid is in the range of about 0.000001 to 0.1 Normal.

7. An aerosol solution formulation according to Claim 3 wherein the weak organic acid is selected from the group consisting of ascorbic acid and citric acid.

8. An aerosol solution formulation according to Claim 3 which contains water in an amount up to about 5.0% wght./wght.

9. An aerosol solution formulation according to Claim 1 wherein the HFC propellant is 1,1,1,2,3,3,3,-heptafluoropropane.

10. An aerosol solution formulation according to Claim 9 wherein the organic cosolvent is ethyl alcohol.

11. An aerosol solution formulation according to Claim 10 wherein the ethyl alcohol is in the range of about 1.0 to 50.0% wght./wght. of the formulation.

12. An aerosol solution formulation according to Claim 10 wherein the strong inorganic acid is selected from

the group consisting of sulfuric acid, hydrochloric acid nitric acid, and phosphoric acid.

13. An aerosol solution formulation according to Claim 12 wherein the strong inorganic acid is in the range of about 0.0000001 to 0.1 Normal.

14. An aerosol solution formulation according to Claim 10 wherein the weak organic acid is selected from the group consisting of ascorbic acid and citric acid.

15. An aerosol solution formulation according to Claim 14 wherein the weak organic acid is in the range of about 0.00015 to 275 mg/ml.

16. An aerosol solution formulation according to Claim 10 which contains water in an amount up to about 0.0 to 5.0% wght./wght.

17. An aerosol solution formulation comprising ipratropium bromide, an HFC propellant, ethyl alcohol and either a strong inorganic acid or weak organic acid.

18. An aerosol solution formulation according to Claim 17 wherein the HFC propellant is 1,1,1,2-tetrafluoroethane.

19. An aerosol solution formulation according to Claim 18 wherein the ethyl alcohol is within the range of about 1.0 to 50.0% wght./wght.

20. An aerosol solution formulation according to Claim 18 wherein the strong inorganic acid is selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, and phosphoric acid.

21. An aerosol solution formulation according to Claim 20 wherein the strong inorganic acid is within the range of about 0.00002 to 0.01 Normal.

22. An aerosol solution formulation according to Claim 18 wherein the weak organic acid is selected from the group consisting of ascorbic acid and citric acid.

23. An aerosol solution formulation according to Claim 22 wherein the weak organic acid is ascorbic acid and

which is within the range of about 0.0045 to 275 mg/ml.

24. An aerosol solution formulation according to Claim 22 wherein the weak organic acid is citric acid and which is within the range of about 0.0039 to 27.7 mg/ml.

25. An aerosol solution formulation according to Claim 17 wherein the HFC propellant is 1,1,1,2,3,3,3-heptafluoropropane.

26. An aerosol solution formulation according to Claim 25 wherein the ethyl alcohol is within the range of about 1.0 to 50.0% wght./wght.

27. An aerosol solution formulation according to Claim 25 wherein the strong inorganic acid is selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, and phosphoric acid.

28. An aerosol solution formulation according to Claim 26 wherein the strong inorganic acid is within the range of about 0.00002 to 0.01 Normal.

29. An aerosol solution formulation according to Claim 25 wherein the weak organic acid is selected from the group consisting of ascorbic acid and citric acid.

30. An aerosol solution formulation according to Claim 29 wherein the weak organic acid is ascorbic acid and which is within the range of about 0.0045 to 275 mg/ml.

31. An aerosol solution formulation according to Claim 29 wherein the weak organic acid is citric acid and which is within the range of about 0.0039 to 27.7 mg/ml.

32. An aerosol solution formulation according to Claim 1 wherein the medicament is selected the group consisting of ipratropium bromide, oxitropium bromide, albuterol, metaproterenol, tiotropium bromide and fenoterol.

33. An aerosol solution formulation according to Claim 32 wherein the HFC propellant is 1,1,1,2-tetrafluoroethane.

34. An aerosol solution formulation according to Claim 33 wherein the cosolvent is ethyl alcohol.

35. An aerosol solution formulation according to Claim 32 wherein the HFC propellant is 1,1,1,2,3,3,3-heptafluoropropane.

36. An aerosol solution formulation according to Claim 35 wherein the cosolvent is ethyl alcohol.

37. An aerosol solution formulation comprising a medicament, an HFC propellant, a cosolvent, and either a strong inorganic acid or weak organic acid, wherein the medicament; is soluble in the propellant/cosolvent system, tends to degrade or decompose based on the interaction between the medicament and the cosolvent or water, and degrades or decomposes by an acid sensitive mechanism such that the rate of degradation or decomposition can be effectively reduced by the addition of acid.

38. An aerosol formulation according to Claim 37 wherein the HFC propellant is 1,1,1,2-tetrafluoroethane and the cosolvent is ethyl alcohol.

39. An aerosol formulation according to Claim 37 wherein the HFC propellant is 1,1,1,2,3,3,3-heptafluoropropane and the cosolvent is ethyl alcohol.

40. A method for stabilizing an aerosol solution formulation wherein the aerosol solution formulation comprises a medicament, 1,1,1,2-tetrafluoroethane and a cosolvent, and wherein the medicament degrades by interaction with the cosolvent or water or other mechanism, such degradation having the capability of being reduced to acceptable levels by the addition of acid, such method comprising the addition of an amount of a strong inorganic acid or weak organic acid to the aerosol solution formulation.

41. A method for stabilizing an aerosol solution formulation wherein the aerosol solution formulation comprises a medicament, 1,1,1,2,3,3,3-heptafluoropropane and a cosolvent, and wherein the medicament degrades by interaction with the cosolvent or water or other mechanism,

such degradation having the capability of being reduced to acceptable levels by the addition of acid, such method comprising the addition of an amount of a strong inorganic acid or weak organic acid to the aerosol solution formulation.

42. In a method of treating a patient by the administration of an aerosol solution formulation the improvement wherein comprises administering said aerosol solution formulation as a stabilized aerosol solution comprising a medicament, 1,1,1,2-tetrafluoroethane, a cosolvent, and either a strong inorganic acid or a weak organic acid.

43. A method of treatment according to Claim 42 wherein said medicament in the stabilized aerosol solution formulation is ipratropium bromide and the cosolvent is ethyl alcohol.

44. In a method of treating a patient by the administration of an aerosol solution formulation the improvement wherein comprises administering said aerosol solution formulation as a stabilized aerosol solution comprising a medicament, 1,1,1,2,3,3,3-heptafluoropropane, a cosolvent, and either a strong inorganic acid or a weak organic acid.

45. A method of treatment according to Claim 44 wherein said medicament in the stabilized aerosol solution formulation is ipratropium bromide and the cosolvent is ethyl alcohol.

IPRATROPIUM BROMIDE AEROSOL SOLUTIONS STABILITY PROFILES
0.84 mg/ml IPBR
35/65% w/w/ EtOH/HFC-134a

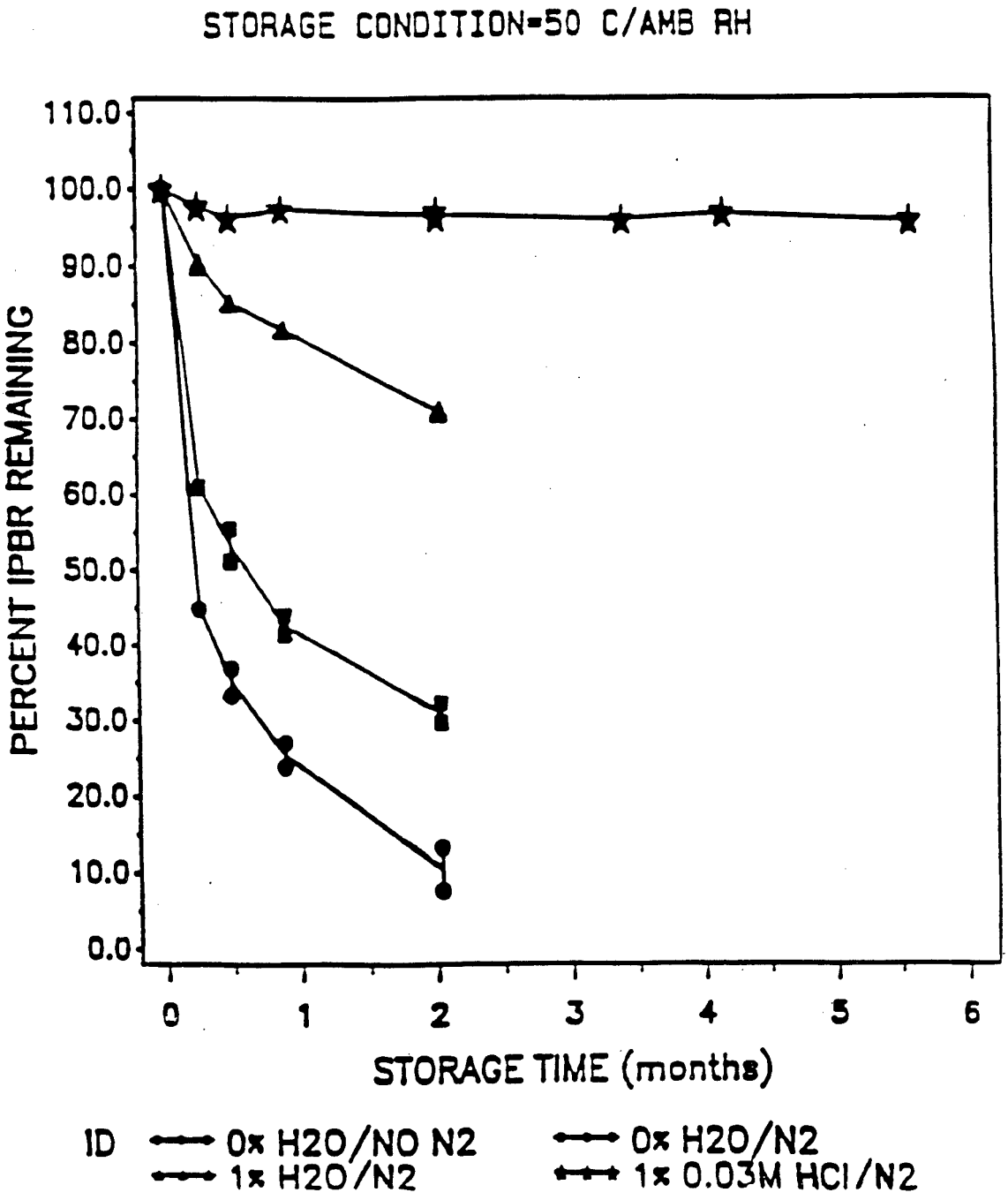

FIGURE 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/11856

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A,2 868 691 (PORUSH I. ET AL) 13 January 1959 see column 2, line 61 - column 3, line 17 see column 4; example 4	1 2-45
Y	EP,A,0 504 112 (CIBA GEIGY AG) 16 September 1992 see page 7; example 7 see page 8; example 20	2-45
X	US,A,3 282 781 (MACEK T.J. ET AL) 1 November 1966 see column 4; example 4	1
X	WO,A,90 07333 (RIKER LABORATORIES) 12 July 1990 see page 12 - page 14; example 4	1-4,7,8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 April 1994	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/11856

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

	Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
2	A	WO,A,91 11495 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH) 8 August 1991 see page 6	1-45
1	A	EP,A,0 372 777 (RIKER LABORATORIES INC) 13 June 1990 cited in the application see page 5, line 28 - line 35 see page 6; example 5	1-45
1	A	WO,A,91 11496 (BOEHRINGER INGELHEIM INTERNATIONAL GMBH) 8 August 1991 cited in the application see page 5; examples 1-3	1-45
1			

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/11856

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
REMARK: Although claims 42-45 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US 93/11856

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-2868691		BE-A-	555319	
		GB-A-	830426	
EP-A-0504112	16-09-92	AU-B-	646723	03-03-94
		AU-A-	1218892	17-09-92
		JP-A-	4327527	17-11-92
US-A-3282781		NONE		
WO-A-9007333	12-07-90	DE-D-	69003804	11-11-93
		EP-A,B	0452384	23-10-91
		JP-T-	4504566	13-08-92
WO-A-9111495	08-08-91	DE-A-	4003272	08-08-91
		AU-A-	7211391	21-08-91
		CA-A-	2075058	04-08-91
		EP-A-	0514415	25-11-92
		JP-T-	5504160	01-07-93
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		ES-T-	2045470	16-01-94
		JP-A-	2200627	08-08-90
		US-A-	5225183	06-07-93
WO-A-9111496	08-08-91	DE-A-	4003270	08-08-91
		AU-A-	7211691	21-08-91
		EP-A-	0513099	19-11-92
		JP-T-	5504350	08-07-93