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(19)

(54) NEW FORM OF FLUNISOLIDE AND THE USE OF FLUNISOLIDE TO TREAT RESPIRATORY DISEASES

(71) We, SYNTEX (U.S.A.) INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 3401 Hillview Avenue, Palo Alto, California 94304, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a unique crystalline form of flunisolide, a process for preparing the novel crystalline form, treatment of respiratory diseases using this form and therapeutically useful preparations containing this unique form.

Flunisolide is the common name of a known compound, 6α - fluoro - 11β,21 - dihydroxy - 16α,17α - isopropylidenedioxypregna - 1,4 - diene - 3,20 - dione. The compound and procedure for making it are described in United States Patent 3,126,375 to Ringold et al (U.K. Specification No. 920,503). It has anti-inflammatory, glycogenic, thymolitic, anti-estrogenic, anti-androgenic, and anti-pruritic activity and has had primary utility in the treatment of topical inflamed conditions. The compound is previously unknown to be polymorphic but it has now been discovered that there are several polymorphic forms, one of which is particularly stable in the presence of aerosol propellants so that it may be readily formulated to form an aerosol which is particularly valuable in the treatment of respiratory diseases such as bronchial asthma, allergic rhinitis, and others which respond to treatment by suitable steroids.

It is generally known in the art that certain specific steroids may be used for the treatment of asthma, for example, hydrocortisone and prednisolone have been used as an aerosol suspension. (See for example *J. Allergy, 29* (3), 214—221, 1958). Other steroids which have been used in various formulations include dexmethasone phosphate (See U.S. 3,282,791 to Macek; *J. Allergy, 34* (2), 119—126, March-April, 1963), betamethasone 17-valerate (see *JAMA, 231* (4), 406—407, January 27, 1975(and triamcinolone acetonide (see *J. Allergy, 33* (1), 1—5, January-February, 1962 and *American Review of Respiratory Disease, 109*, 538—543, 1974). It is also known that beclomethasone dipropionate (9α - chloro - 16β - methyl - prednisolone - 17α,21 - dipropionate) along with certain other steroids such as fluocinolone acetonide (6α,9α - difluoro - 11β,21 - dihydroxy - 16α,17α - isopropylidenedioxy - pregna - 1,4 - diene - 3,20 - dione) may be used in aerosol formulations as taught in German Offenlegungsschrift 2,320,111 (U.K. Specification No. 1,429,184). However, that patent teaches that if these steroids are placed in the aerosol formulation without previous treatment the particles tend to increase in size and deposit on the sides of the can or along the throat of the release tube and may ultimately plug the tube or change the concentration of the aerosol released. Thus, that patent teaches that if the steroid is first solvated according to the process described, the solvated steroid does not tend to increase in particle size nor drop out of the dispersion in the aerosol formulation.

It has now been found that flunisolide is useful in the treatment of respiratory diseases such as bronchial asthma, allergic rhinitis, nasal polyps, and the like. It has also been found that a unique crystalline form of flunisolide may be prepared which is stable in aerosol formulations which use suitable fluorinated and chlorinated hydrocarbon propellants. This heretofore unknown crystalline form may be prepared by contacting any of the other polymorphic forms of flunisolide with a suitable solvent for a sufficient period

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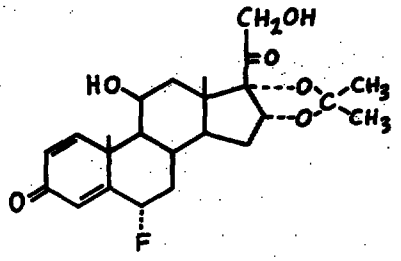
of time to form the crystalline form which is readily dispersed for use in the treatment of bronchial asthma, allergic rhinitis or other respiratory ailments.

The compound which is useful in the process of this invention for human respiratory disorders is 6α - fluoro - 11β,21 - dihydroxy - 16α,17α,2' - propylidenedioxy - pregna - 1,4 - diene - 3,20 - dione (hereafter Flunisolide) represented by the following formula:



The unique crystalline form of this invention is referred to hereafter as form A. One aspect of this invention provides form A of flunisolide, a process for preparing it, and pharmaceutical compositions containing it. The particle size of the unique crystalline form is suitably less than 100 microns (98% or more of the particles being less than 100 microns), and preferebly less than 25 microns. The particle size range of up to 10 microns is best for uniform dispersion of form A in a suitable fluorinated and chlorinated hydrocarbon. The crystal structure has an X-ray diffraction pattern as indicated in Table A, below.

TABLE A

d Å	I/I₁ %	θ deg.
10.04	50	4.4
9.82	60	4.5
9.30	80	4.8
7.69	50	5.8
6.91	50	6.4
6.32	10	7.0
5.98	90	7.4
5.53	100	8.0
5.21	60	8.5
5.06	60	8.8
4.79	10	9.3
4.55	70	9.8
4.33	1	10.3
4.13	10	10.8
3.95	10	11.3
3.86	5b	11.5
3.70	5	12.0
3.63	10	12.3
3.36	1	13.3
3.30	2	13.5
3.21	2	13.9
3.03	1	14.8
2.88	2	15.5
2.67	2b	16.8
2.63	1	17.0
2.60	1	17.3
2.56	1	17.5
2.40	3	18.8
2.31	1	19.5
2.28	1	19.8
2.13	1	21.3
2.10	1	21.5
1.97	1	23.0
1.88	2	24.3

A general discussion of the theory and definitions as well as the general procedure of X-ray diffractometry is set forth in the monograph at pages 902—904 of the *National Formulary XIII*.

The above X-ray diffraction pattern was made using a Siefert Debeyflex Universal X-ray generator Catalog No. 2200 having a copper anode tube with a nickel filter and a 35 mm Nonius camera having a 114.6 mm diameter. The readings were taken using the ground powder of flunisolide placed in a suitable capillary tube having an inside diameter of about 0.5 mm mounted in the X-ray beam. The crystal structure of the ground flunisolide exhibits a regular 3-dimensional pattern in which the atoms and molecules of which are packed together. In the above diffraction pattern the symbol "d" is the interplanar spacing, that is the distance between parallel planes in which the atoms of the crystal lie. The spacing between the planes in the 3-dimensional lattice it determined from the X-ray diffraction. The dimensions of the spacings are given in terms of angstroms (Å). "θ" is one half the angle between the primary beam projection and the diffracted beam while the ratio "I/I_1" is the relative intensity of an X-ray maxima in which "I" is the intensity of the maximum corresponding to the indicated "d" value, and "I_1" is the intensity of the strongest maximum of the pattern. The intensities in this case in which a film was used was compared with a calibrated scale.

As pointed out in the above monograph in the *National Formulary XIII*, in powder diffraction work, intensity data are intended only as a guide to strong and weak X-ray maximum. They may vary much from laboratory to laboratory by as much as about 25%. Further, the errors in data for interplanar spacings ("d" value) vary according to the size of the spacing. The error in "d" is inversely proportional to "θ". Variation of the observed "d" value from those given in the Table A are permissible up to a magnitude equivalent to $\pm 0.3°\ \theta$ (for a copper target X-ray tube), which was used in the determination of form A.

As pointed out previously it was not here-to known that flunisolide existed in polymorphic

forms, thus each of the forms defined hereinafter are newly recognized entities.

Form A of flunisolide may be obtained either (1) by recrystallizing the compound from a suitable, aprotic, non-polar solvent or (2) by contacting micronized particles of any of the other polymorphic forms of flunisolide with a suitable liquid, aprotic, non-polar compound in which the flunisolide does not dissolve to any substantial extent, typically a liquid halogenated alkane, for a period of time sufficient to convert the other polymorphic form to form A.

It will be recognized by one acquainted with solutions that a compound loses its crystalline identity when going into solutions. It has been found that Form A is the form which is taken whenever flunisolide is recrystallized from a solution in a suitable solvent. The flunisolide must, of course, be substantially soluble in the solvent from which Form A is precipitated.

Particularly valuable as solvents from which Form A is recrystallized include the halogenated hydrocarbon solvents which are liquids at room temperature, particularly the chlorinated lower aliphatic hydrocarbons, for example methylene chloride. The process simply entails dissolving any of polymorphic forms of flunisolide in a suitable solvent and forcing the crystallization of the flunisolide to develop Form A. The crystallization may be done by forcing the flunisolide out of solution, e.g. by adding another solvent in which flunisolide is less soluble, such as a suitable aliphatic or aromatic liquid hydrocarbon. Suitable aromatic hydrocarbons include benzene and toluene, while suitable aliphatic hydrocarbons includes those of medium carbon chain length, e.g. 6—12 carbons and may be branched or straight hydrocarbon. Examples are iso-octane, hexane, heptane, nonane, decane and octane. Iso-octane is particularly effective, i.e. 2,2,4 - trimethyl pentane.

The conversion of flunisolide to Form A by contacting any other micronized polymorphic form of flunisolide with a suitable non-solvent liquid was truly surprising since in such a process, the crystalline structure of the other polymorphic forms is not eliminated by solution, but it appears that form A is formed by an internal crystalline rearrangement without an intermediate destruction of the old crystalline structure and without further particle growth. Compounds found to be particularly valuable for effecting the conversion are the halogenated lower aliphatic hydrocarbons, especially those known as the Freons, a trademark for a group of halogenated hydrocarbons (usually based on methane or ethane) containing one or more fluorine atoms widely used as non-toxic propellants. Particularly useful are, Freon 12, Freon 114 and mixtures of these two as well as mixtures of these two with other Freons such as Freon 11, Freon 22, Freon 113, Freon 21, Freon 13, Freon C318 and Freon 115 (as identified later). Other compounds which may be included are non-toxic, lower alkanes containing up to 5 carbons such as butane or pentanes.

Form A may be prepared either prior to forming the aerosol formulation or it may be prepared by contacting a micronized form in a suitably-sized particle with the propellant under conditions suitable for maintaining the propellant as a liquid. Since the unique form A of flunisolide is formed by contact with certain liquid propellants (e.g. Freons 12 and 114) which are ultimately used for the formulation, it may not be necessary to first prepare Form A before formulating. All that is required is to micronize the flunisolide to the desired particle size, i.e. less than about 100 microns, more suitably less than about 25 microns and preferably less than about 5 microns.

It appears that the conversion of the other polymorphic forms of flunisolide to form A begins soon after contact with the suitable liquid compound. Substantially complete conversion is obtained in two weeks at room temperature and about 50 psig in the Freons. Since the Freons are generally gaseous at room temperature care must be taken to employ conditions which will retain the Freons as a liquid. Thus temperatures below their boiling point must be employed or the compounds must be kept under pressure sufficient to maintain the compounds as liquids. This is generally done simply by employing methods known in the art for preparing aerosols. The flunisolide is first micronized to the desired particle size and the aerosol "bombs" or dispensers are prepared according to known methods as discussed hereafter. Thus, if the flunisolide is not in Form A to begin with, the conversion takes place after the aerosol dispenser is prepared.

As pointed out previously, it has been found that the form A is formed by contacting any of the other polymorphic forms of flunisolide with the suitable solvent as delineated above. It is surprising to find that this occurs since form I upon heating up to about 200° and cooling the flunisolide back to room temperature will be transformed into form B which seems to be the most stable form as a free solid, that is under air. Form B has the X-ray diffraction pattern as set forth in Table B.

TABLE B

d Å	I/I_1	θ deg.
8.84	1	5.0
7.82	80	5.6
7.08	60	6.3
6.80	60	6.5
6.32	70	7.0

TABLE B (cont.)

6.10	80	7.3
5.90	80	7.5
4.79	100	9.3
4.44	100	10.0
4.13	1	10.8
3.78	1	11.8
3.49	1	12.8
3.08	5	14.5
2.88	1	15.5
1.78	50	26.0
1.73	2	26.5
1.70	2	27.0

Another polymorphic form referred to herein as form C also exists which may be substantially pure flunisolide or it may exist with a certain amount of methanol included in the holes of this particular crystal lattice, thus forming a methanol chlathrate. The X-ray diffraction pattern of form C is given in Table C. Form C may also be converted into stable form B upon heating to 200°C and cooling to room temperature.

TABLE C

d	I/I_1	θ
Å		deg.
13.59	10	3.3
8.84	1	5.0
7.37	20	6.0
6.65	100	6.6
6.10	2	7.3
5.43	80	8.2
4.92	5	9.0
4.67	5	9.5
4.13	10	10.8
3.78	1	11.8
3.52	5	12.6
3.19	1	14.0
3.13	1	14.3
2.88	1	15.5
2.79	1	16.0

Treatment of Respiratory Diseases

Another aspect of this invention provides flunisolide as an atomisable solution in a pharmaceutically acceptable solvent suitable for nasal or inhalation administration, and containers containing such compositions and adapted for nasal or inhalation administration of their contents. Treatment comprises administering by inhalation a therapeutically effective amount of flunisolide to a person having a respiratory disease which responds to such treatment. The inhalation may be either bronchially via the oropharynx (orally) or nasally but is such that a sufficient amount of the compound comes in contact with the afflicted area to cause an improvement in the condition. The portion of the respiratory tract afflicted may be the nasal chambers, trachae, bronchi, lower air passages, or brochioles.

It appears that flunisolide is effective in the treatment of bronchial asthma, bronchitis, pneumonitis, occupational lung disease, allergic rhinitis, nasal polyps, and seasanol hay fever.

In treating respiratory tract allergies which are located generally primarily in the nasal area such as allergic rhinitis, nasel polyps or seasonal hay fever, a therapetically effective amount of Flunisolide is sprayed into the nasal chamber optionally while the person is inhaling through the nose, inhalation not being necessary in each case. In the case of affliction of the trachea, bronchi or bronchioles, the active ingredient is most effectively administered by releasing a metered dosage of aerosol (i.e., a gaseous suspension of solid particles) within the mouth of the patient and having the patient inhale at substantially the same time so that the mist is taken into the mouth and the active ingredient is administered to the respiratory tract.

Generally a therapeutically effective amount for nasal afflictions is about 0.01 milligrams (mg.) to about 5.0 mg per person per day, preferably 0—.05 to 0.25, while for other respiratory diseases about .5 mg to about 5 mg. per person per day and preferably 1 to 2 mg. per person per day is effective. The amount may be administered all at one time or in several smaller portions at designated times during the day. The smaller portions may be anywhere from 0.01 to 1.0 mg. per dosage. The exact dosage will vary with, i.e., the severity of the condition, the particular formulation used, other drugs used, and the individual involved.

Flunisolide may be formulated using any method that is generally known in the art such as an aerosol or an atomizable liquid and thus may be a solution, dispersion or suspension in a suitable liquid carrier packaged under super atmospheric pressure with a gaseous propellant for release as a gaseous suspension of, e.g. solid particles (aerosol) or packaged under atmospheric pressure as a squeeze bottle or an atomizer, a rigid bottle equipped with a pump valve for dispersal of liquid droplets.

Thus a preferred aspect of this invention is 6α - fluoro - 11β,21 - dihydroxy - 16α,17α - isopropylenedioxypregna - 1,4 - diene - 3,20 - dione of a particle size of less than 100 microns, preferably less than 25 microns, in particular less than 10 microns, in an aerosol composition containing 0.001 to 20% by weight (calculated on the basis of the total composition) of said steroid, said composition being in a container adapted for administration via inhalation. In this respect the definition of a particle size of less than 100 microns (or less than 25, or less than 10 microns) implies that at least 89% of the considered particles have dimensions ranging between the size of a single molecule (and

(14)

therefore includes solutions) and the size of an aggregate of molecules, said aggregate having a dimension of less than 100 microns (or less than 25, or less than 10 microns, respectively).

In the case of aerosols, contrary to the teaching of the German Specification which requires the solvation of beclamethasone dipropionate or fluocinolone acetonide before formulation, flunisolide need not be solvated prior to formulation since, surprisingly, it does not appear to be plagued with problems of crystal growth in the aerosol formulation.

Generally, if an aerosol is employed the flunisolide will be a finely-divided solid material or powder suspended in a suitable liquidified propellant which also serves as a suspending medium with a non-ionic surface active agent which is a liquid at ambient temperatures. Typical of the self-propelling powder dispensing compositions which are known in the art are those disclosed in U.S. Specification 3,014,844 to Thiel et al or U.S. Specification 3,322,625 to Shimmin.

More specifically, in the aerosol compositions which are useful in the process of this invention the active ingredient is generally a finely divided powder and may constitute from about 0.01 to about 20% by weight of the total composition. A particularly suitable range is about 0.05 to about 10% and preferably the range will be about 0.1 to about 3% by weight of the total composition.

Generally, the particle size of the finely divided solid powder should be large enough so that they are deposited in the respiratory tract and not exhaled by the patient after inhalation. Also, for best results, the size of the particles of powder should be substantially uniform.

Also present is a surface active agent which may constitute from about 0.1 to about 20% by weight, desirably between 0.25 and 5%, and preferably for purposes of treating respiratory diseases between about 0.25 and 1% by weight of the total composition, the remainder of the composition being the liquifield propellant.

The surfactant employed is preferably a liquid, non-ionic, surface-active agent and should have an hydrophile-lipophile balance (HLB) ratio of less than 10. The HLB ratio is an empirical number which provides a guide to the surface-active properties of a surface-active agent. The lower the HLB ratio, the more lipophilic is the agent, and conversely, the higher the HLB ratio, the more hydrophilic is the agent. The HLB ratio is well known and understood by the colloid chemist and its method of determination is described by W. C. Griffin in the Journal of the Society of Cosmetic Chemists, vol. 1, No. 5, pages 311—326 (1949). Preferably the surface-active agent employed should have an HLB ratio of about 1 to 5. It is possible to employ surface-active agents which themselves do not possess an HLB ratio within these ranges, providing they are used in conjunction with other surface-active agents which have an HLB ratio which will provide a mixture having an HLB ratio within the prescribed range.

Those surface-active agents which are soluble or dispersable in the propellant are effective. The more propellant-soluble surface-active agents are the most effective. It is also important that the surface-active agent should be non-irritating and non-toxic.

We have found that among the liquid non-ionic surface-active agents which may be employed in our compositions are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octoic, lauric, palmitic, stearic, linoleic, linolenic, eleostearic and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride such as, for example, ethylene glycol, glycerol, erythritol, arabitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol (the sorbitan esters sold under the trademark "Spans") and the polyoxyethylene and polyoxypropylene derivatives of these esters. Mixed esters, such as mixed or natural glycerides may be employed. The preferred surface-active agents are the oleates of sorbitan, e.g., those sold under the trademarks "Arlacel C" (Sorbitan sesquioleate), "Span 80" (sorbitan monooleate) and "Span 85", (sorbitan trioleate).

Specific examples of other surface-active agents which may be employed are

Sorbitan monolaurate
Polyoxyethylene sorbitol tetraoleate
Polyoxyethylene sorbitol pentaoleate

The liquified propellant employed is one which is a gas at room temperature (65°F.) and atmospheric pressure (760 mm. of mercury), i.e., it shall have a boiling point below 65°F. at atmospheric pressure and is non-toxic. Among the suitable liquified propellants which may be employed are the lower alkanes containing up to five carbon atoms, such as butane and pentane. The most suitable liquified propellants are the fluorinated and fluorochlorinated lower alkanes such as are sold under the trademark "Freon". Mixtures of the above mentioned propellants may suitably be employed.

It is contemplated that the fluorinated or fluorochlorinated lower alkane shall contain not more than four carbon atoms and at least one fluorine atom. The preferred halogenated lower alkane compounds may be represented generally by the formula $C_mH_nCl_yF_z$, wherein m is an integer less than 5, n is an integer or zero, y is an integer or zero, and z is an integer, such that $n+y+z=2m+2$. Examples of these propellants are dichloro-

difluoro methane ("Freon 12"), dichlorotetrafluoroethane ("Freon 114"), monochloropentafluoroethane ("Freon 115"), trichloromonofluoromethane ("Freon 11"), dichloromonofluoromethane ("Freon 21"), monochlorodifluoromethane ("Freon 22"), trichlorotrifluoroethane ("Freon 113"), octafluorocyclobutane ("Freon C318"), and monochlorotrifluoromethane ("Freon 13"). Propellants with improved vapor pressure characteristics may be obtained by using certain mixtures of these compounds, e.g. "Freon" with "Freon 12" or "Freon 12" with "Freon 114". For example, dichlorodifluoromethane, which has a vapor pressure of about 70 pounds per square inch gauge and 1,2 - dichloro - 1,2,2 - tetrafluoroethane ("Freon 114", with a vapor pressure of about 13 pounds per square inch gauge at 70°F., may be mixed in various proportions to form a propellant having an intermediate vapor pressure which is well suited for use in relatively low pressure containers.

It is most desirable that the vapor pressure of the propellant employed shall itself be between about 25 and 65 pounds per square inch gauge at 70°F., and preferably between about 30 and 40 pounds per square inch gauge at that temperature. A one-component propellant defined for use in the composition may give a composition with gauge pressures in the range of 55 to 65 pounds per square inch at 70°F., which are usable safely with metal containers. The two-component propellants, such as equal weight mixtures of "Freon 12" and "Freon 11", may give gauge pressures in the range of 20 to 40 pounds per square inch at 70°F, which are usable safetly with specially reinforced glass containers.

It is usually desirable to keep the gas pressure as low as possible, within the limits imposed by the desired specific gravity of the propellant, in order to enable simple containers to be used safely and to prevent too high a pressure causing too wide a dispersal of the powder aerosol. When stronger containers, for example of stainless steel, can be used and the active solid medicament is intended for pulmonary inhalation, it is advantageous to use a propellant with a gauge pressure of between 40 and 50 pounds per square inch; this allows complete aerosolization before the stream reaches the back of the throat. Since the powder is already present in the composition dispersed in the desired particle size, there is no need for further breakup action in the valve or applicator, so valves of simple construction may be used, and there is no need to provide special nozzles and expansion chambers, as is usually required when dispensing materials which are dissolved in the propellant, or in a liquid which is emulsified with the propellant.

In producing the aerosols which are useful in the process of this invention, a container equipped with a suitable valve is first filled with a propellant containing the finely-divided powder in suspension. A container may first be charged with a weight amount of dry powder which has been ground to a predetermined particle size or in a slurry of powder in the cooled liquid propellant. Alternately and preferably, the powder in the surface active agent may be triturated or homogenized first into a uniform paste, for instance, by pestle and mortar. This paste is then dispersed in the cooled liquified propellant. This procedure fosters uniform wetting of the powder particles. A container may also be filled by introducing powder and propellant by the normal filling method or a slurry of the powder in that component of the propellant which boils above room temperature may be placed in the container, the valve sealed in place, and the balance of the propellant may be introduced by pressure filling through the valve nozzle. On operating the valve, the powder will be dispensed in a stream of propellant which will vaporize providing aerosol dry powder. The amount provided by each operation of the valve may be metered according to any method known in the art. Throughout the preparation of the product care is desirably exercised to minimize the absorption of moisture where the powder is adversely affected by the water. This may be readily accomplished by operating in a dehumidified atmosphere using only dry materials and equipment.

Suitably, nasal disorders such as allergic rhinitis, nasal polyps, or seasonal hay fever may be treated with an aerosol formulation as discussed hereinbefore or with an atomizable liquid solution of flunisolide. If an aerosol is employed, the outlet will be adapted for release into the nasal passage instead of into the mouth. Such adaptations are well known in the art.

A liquid solution of flunisolide on the other hand is readily dispensed from a flexible squeeze bottle or other atomizing device. The composition of the nasal spray solution may suitably comprise about 0.001 to 0.1%w Flunisolide, 0 to 50%w of a suitable organic solvent, 0 to 5%w suitable pharmaceutical excipients, and the remainder water. The solution is preferably isotonic and will have a pH of about 4.0—8.0, especially pH about 5.0—7.0.

Suitable organic solvents include nontoxic glycols, alcohols, or compatible mixtures thereof. Satisfactory glycol solvents include propylene glycol; polyethylene glycol, of molecular weight (MW) 200 to 20,000; glycerol, butylene glycol and hexylene glycol. Of these, propylene glycol, polyethylene glycol of M.W. 3,000—10,000, and mixtures thereof are preferred. Suitable alcohol solvents include isopropyl alcohol and ethanol.

Suitable pharmaceutical excipients include

substances which are non-toxic and known to be effective in preventing microbial growths (preservatives), in maintaining the proper pH (buffering agents), in preventing oxidation (anti-oxidants), or in otherwise increasing or maintaining the effectiveness of the solution.

Suitable preservatives include benzalkonium chloride, chloroethanol, methyl paraben, propyl paraben, and others known to anyone familiar in the art. Suitable buffering agents include inorganic or organic acid-base pairs such as citrate, phosphate and tartrate, preferably citrate buffer. Suitable antioxidants include citric acid, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and propyl gallate.

A particularly valuable formulation for a nasal spray comprises 0.001%w to 0.01%w flunisolide, 0 to 20% polyethylene glycol 6000, 15 to 20% propylene glycol, suitable excipients 0.01 to 1.0%w, and the remainder water, adjusted to pH 6.0±1.0.

The procedure for preparing the solution for nasal application comprises first dissolving flunisolide in the solvent, next dissolving the excipients in water, and finally mixing the two solutions.

Following are examples of formulations which are useful for use in the process of this invention. The examples are given solely to be illustrative and are intended neither to delineate the scope of the invention nor limit the ambit of the appended plains. In the case of aerosols the formulations are representative of flunisolide in combination with an effective amount of propellant (carrier) and surface active agents, while the nasal sprays are representative of typical aqueous formulations of flunisolide in combination with pharmaceutically effective amounts of suitable solvents and excipients. All percentages are by weight.

Example I—Aerosol

	Percent
Flunisolide (particle size range of 1 to 5 microns)	3.0
Span 85 (sorbitan trioleate)	1.0
Freon 11 (trichloromonofluoromethane)	30.0
Freon 114 (dichlorotetrafluoroethane)	41.0
Freon 12 (dichlorodifluoromethane)	25.0

Example II—Aerosol

	Percent
Flunisolide, (particle size range of 1—5 microns)	0.5
Span 85	0.5
Propellant B*	99.0

*Propellant B consists of 10% Freon 11, 50.4% Freon 114, 31.6% Freon 12, and 8.0% butane.

Example III—Aerosol

	Percent
Flunisolide	1.00
Span 85	0.25
Freon 11	5.0
Freon W*	93.75

*Freon W consists of 61.5% Freon 114 and 38.5% Freon 12.

Example IV—Aerosol

	Percent
Flunisolide	0.50
Span 80	0.50
Propellant C*	99.0

*Propellant C consists of 30.0% Freon 11 and 70% Freon W.

Example V—Aerosol

	Percent
Flunisolide	0.88
Span 85	1.00
Propellant consisting of 50% Freon 12, 25% Freon 11, and 25% Freon 114	98.12

Example VI—Nasal Spray Solution

	Percent
Flunisolide	.025
Polyethylene glycol 6000	15.0
Propylene glycol	20.0
Benzalkonium chloride	0.01
Citric acid (anhydrous)	0.05
Water q.s. ad	100

pH adjusted to 6.0±1.0

Example VII—Nasal Spray Solution

	Percent
Flunisolide	0.01
Sodium chloride	0.7
Propylene glycol	20.0
Benzalkonium chloride	0.01
Water q.s. ad	100.00

Example VIII—Nasal Spray Solution

	Percent
Flunisolide	0.01
95% Ethanol USP	7.00
Sodium chloride	0.8
Benzalkonium chloride	0.01
Water q.s. ad	100.00

Example IX—Preparation of Form A

122 Grams of flunisolide, a mixture of primarily Form B with some Form A material, was dissolved in 800 ml methylene chloride and filtered to remove any solid material. To the resulting solution 1200 ml of iso-octane (2,2,4 - trimethyl pentane) was added and allowed to stand at room temperature for two hours. The resulting solution was evaporated to 1000 ml and allowed to stand overnight at room temperature. The resuting precipitate was filtered, dried, then analyzed via X-ray

diffractometer as discussed herein. The precipitate was found to have substantially the same X-ray diffraction pattern as set forth in Table A above, even after micronization.

Example X—Preparation of Form A

The same procedure as set forth in Example VII was followed except that the solution of flunisolide in methylene chloride was poured into the iso-octane. Upon X-ray analysis, the resulting precipitate was found to have substantially the same X-ray diffraction pattern as set forth in Table A.

WHAT WE CLAIM IS:—

1. A form of flunisolide having an X-ray diffraction pattern substantially as shown in Table A.

2. A form of flunisolide according to claim 1 and of particle size less than 100 microns.

3. A pharmaceutical composition comprising the form of flunisolide of claim 2 with a pharmaceutically acceptable diluent or carrier.

4. A pharmaceutical composition according to claim 3 wherein the diluent or carrier comprises a liquid aerosol propellant.

5. A pharmaceutical composition according to claim 4 wherein said aerosol propellant is a halogenated hydrocarbon containing one or more fluorine atoms or a mixture of such halogenated hydrocarbons.

6. A pharmaceutical composition according to claim 5 wherein the aerosol propellant is selected from dichlorodifluoromethane, dichlorotetrafluoroethane and mixtures thereof.

7. A pharmaceutical composition according to claim 5 wherein the aerosol propellant consists of 50% by weight dichlorodifluoromethane, 25% by weight trichloromonofluoromethane and 25% by weight dichlorotetrafluoroethane.

8. A pharmaceutical composition according to any one of claims 4 to 7 wherein the flunisolide is present in an amount of from 0.001 to 20% by weight of the total composition.

9. A pharmaceutical composition according to any one of claims 3 to 8 wherein the flunisolide is of particle size less than 25 microns.

10. A pharmaceutical composition according to claim 9 wherein the flunisolide is of particle size less than 10 microns.

11. A pharmaceutical composition according to claim 3 substantially as exemplified herein.

12. A pharmaceutical composition comprising flunisolide as an atomizable solution in a pharmaceutically acceptable solvent suitable for nasal administration or administration by inhalation.

13. A pharmaceutical composition according to claim 12 wherein the solution comprises 0.001 to 1% by weight of flunisolide, 0 to 50% by weight of an organic solvent, 0 to 5% by weight of pharmaceutical excipients, and the remainder water.

14. A pharmaceutical composition according to claim 12 wherein the solution is isotonic and has a pH of 4.0 to 8.0.

15. A pharmaceutical composition according to claim 14 wherein the solution has a pH of from 5.0 to 7.0.

16. A pharmaceutical composition according to claim 12 wherein the solution comprises 0.001% to 0.01% by weight flunisolide, 0 to 20% by weight polyethylene glycol 6000, 15 to 20% by weight propylene glycol, 0.01 to 1.0% by weight excipients, and the remainder water, adjusted to pH 5.0 to 7.0.

17. A pharmaceutical composition according to claim 12 substantially as exemplified herein.

18. A pharmaceutical composition according to any one of claims 12 to 17 wherein the flunisolide comprises the form defined in claim 1.

19. A process for preparing the form of flunisolide defined in claim 1 which comprises contacting a polymorphic form of flunisolide with a suitable liquid halogenated alkane which is not a solvent for flunisolide and maintaining said contact until substantially all of said polymorphic form has been converted to the crystalline form as defined in claim 1.

20. A process according to claim 19 wherein said alkane is dichlorodifluoromethane, dichlorotetrafluoroethane, or a mixture thereof.

21. A process for preparing the form of flunisolide defined in claim 1 which comprises dissolving any polymorphic form of flunisolide in a suitable halogenated hydrocarbon, liquid solvent and crystallizing the form of flunisolide of claim 1 from said solvent.

22. A process according to claim 21 wherein said solvent is methylene chloride.

23. A process according to claim 19 or claim 21 substantially as herein described and exemplified.

24. A form of flunisolide as defined in claim 1 when prepared by a process according to any one of claims 19 to 22.

25. A form of flunisolide as defined in claim 1 when prepared by a process according to claim 23.

26. A pharmaceutical composition according to any one of claims 3 to 8 containing flunisolide of claim 24.

27. A pharmaceutical composition according to any one of claims 9 to 17 containing flunisolide of claim 25.

28. A pharmaceutical composition according to any one of claims 3 to 8 or 26 in a container adapted for nasal administration or administration of its contents by inhalation.

29. A pharmaceutical composition according to any one of claims 9 to 17 or 27 in a

diffractometer as discussed herein. The precipitate was found to have substantially the same X-ray diffraction pattern as set forth in Table A above, even after micronization.

Example X—Preparation of Form A

The same procedure as set forth in Example VII was followed except that the solution of flunisolide in methylene chloride was poured into the iso-octane. Upon X-ray analysis, the resulting precipitate was found to have substantially the same X-ray diffraction pattern as set forth in Table A.

WHAT WE CLAIM IS:—

1. A form of flunisolide having an X-ray diffraction pattern substantially as shown in Table A.

2. A form of flunisolide according to claim 1 and of particle size less than 100 microns.

3. A pharmaceutical composition comprising the form of flunisolide of claim 2 with a pharmaceutically acceptable diluent or carrier.

4. A pharmaceutical composition according to claim 3 wherein the diluent or carrier comprises a liquid aerosol propellant.

5. A pharmaceutical composition according to claim 4 wherein said aerosol propellant is a halogenated hydrocarbon containing one or more fluorine atoms or a mixture of such halogenated hydrocarbons.

6. A pharmaceutical composition according to claim 5 wherein the aerosol propellant is selected from dichlorodifluoromethane, dichlorotetrafluoroethane and mixtures thereof.

7. A pharmaceutical composition according to claim 5 wherein the aerosol propellant consists of 50% by weight dichlorodifluoromethane, 25% by weight trichloromonofluoromethane and 25% by weight dichlorotetrafluoroethane.

8. A pharmaceutical composition according to any one of claims 4 to 7 wherein the flunisolide is present in an amount of from 0.001 to 20% by weight of the total composition.

9. A pharmaceutical composition according to any one of claims 3 to 8 wherein the flunisolide is of particle size less than 25 microns.

10. A pharmaceutical composition according to claim 9 wherein the flunisolide is of particle size less than 10 microns.

11. A pharmaceutical composition according to claim 3 substantially as exemplified herein.

12. A pharmaceutical composition comprising flunisolide as an atomizable solution in a pharmaceutically acceptable solvent suitable for nasal administration or administration by inhalation.

13. A pharmaceutical composition according to claim 12 wherein the solution comprises 0.001 to 1% by weight of flunisolide, 0 to 50% by weight of an organic solvent, 0 to 5% by weight of pharmaceutical excipients, and the remainder water.

14. A pharmaceutical composition according to claim 12 wherein the solution is isotonic and has a pH of 4.0 to 8.0.

15. A pharmaceutical composition according to claim 14 wherein the solution has a pH of from 5.0 to 7.0.

16. A pharmaceutical composition according to claim 12 wherein the solution comprises 0.001% to 0.01% by weight flunisolide, 0 to 20% by weight polyethylene glycol 6000, 15 to 20% by weight propylene glycol, 0.01 to 1.0% by weight excipients, and the remainder water, adjusted to pH 5.0 to 7.0.

17. A pharmaceutical composition according to claim 12 substantially as exemplified herein.

18. A pharmaceutical composition according to any one of claims 12 to 17 wherein the flunisolide comprises the form defined in claim 1.

19. A process for preparing the form of flunisolide defined in claim 1 which comprises contacting a polymorphic form of flunisolide with a suitable liquid halogenated alkane which is not a solvent for flunisolide and maintaining said contact until substantially all of said polymorphic form has been converted to the crystalline form as defined in claim 1.

20. A process according to claim 19 wherein said alkane is dichlorodifluoromethane, dichlorotetrafluoroethane, or a mixture thereof.

21. A process for preparing the form of flunisolide defined in claim 1 which comprises dissolving any polymorphic form of flunisolide in a suitable halogenated hydrocarbon, liquid solvent and crystallizing the form of flunisolide of claim 1 from said solvent.

22. A process according to claim 21 wherein said solvent is methylene chloride.

23. A process according to claim 19 or claim 21 substantially as herein described and exemplified.

24. A form of flunisolide as defined in claim 1 when prepared by a process according to any one of claims 19 to 22.

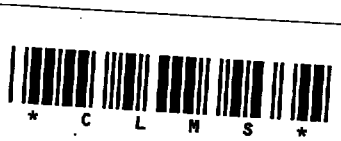
25. A form of flunisolide as defined in claim 1 when prepared by a process according to claim 23.

26. A pharmaceutical composition according to any one of claims 3 to 8 containing flunisolide of claim 24.

27. A pharmaceutical composition according to any one of claims 9 to 17 containing flunisolide of claim 25.

28. A pharmaceutical composition according to any one of claims 3 to 8 or 26 in a container adapted for nasal administration or administration of its contents by inhalation.

29. A pharmaceutical composition according to any one of claims 9 to 17 or 27 in a



container adapted for nasal administration or administration of its contents by inhalation.

30. A container adapted for nasal administration or administration of its contents by inhalation, and containing a pharmaceutically acceptable atomizable liquid composition comprising flunisolide.

31. A container according to claim 30 wherein the composition comprises 0.001% to 0.1% by weight of flunisolide, 0 to 50% by weight of a pharmaceutically acceptable organic solvent, 0 to 5% by weight of pharmaceutical excipients, and the remainder water.

32. A container according to claim 31 wherein the composition is an isotonic solution.

33. A container according to any one of claims 30 to 32 wherein the composition is a solution of pH 4.0 to 8.0.

34. A container according to claim 33 wherein the solution is of pH 5.0 to 7.0.

35. A container according to claim 30 wherein the composition is a solution comprising 0.001 to 0.01% by weight flunisolide, 0 to 20% by weight polyethylene glycol 6000, 15 to 20% by weight propylene glycol, 0.01 to 1.0% by weight excipients and the remainder water adjusted to pH 5.0 to 7.0.

36. A container according to claim 30 wherein the composition comprises undissolved flunisolide, the undissolved flunisolide being of particle size less than 100 microns.

37. A container according to claim 36 wherein the undissolved flunisolide is of particle size less than 10 microns.

38. A container according to claim 36 wherein the undissolved flunisolide is of particle size less than 25 microns.

39. A container according to any one of claims 36, 37 and 38, wherein the composition is in aerosol form.

40. A container according to any one of claims 30 to 39 wherein the flunisolide is present in an amount of from 0.001 to 20% by weight of the total composition.

41. A container according to claim 30 wherein the composition is substantially as exemplified herein.

MEWBURN, ELLIS & CO,
Chartered Patent Agents,
70/72, Chancery Lane,
London, WC2A 1AD,
Agents for the Applicants.

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* C L M S *

ERRATA

SPECIFICATION No. 1,525,181

Page 1, line 49, *after* 1975 *delete* (*insert*)
Page 2, line 87, *for* it *read* is
Page 2, line 115, *after* not *delete* here-to *insert* heretofore
Page 3, line 16, *for* solutions *read* solution
Page 4, line 59, *for* trachae *read* trachea
Page 4, line 64, *for* seasanol *read* seasonal
Page 4, line 68, *for* nasel *read* nasal
Page 4, line 69, *for* therapetically *read* therapeutically
Page 4, line 94, *for* i.e., *read* i.a.,
Page 4, line 123, *for* 89% *read* 98%
Page 5, line 47, *for* liquifield *read* liquified
Page 6, line 16, *for* 1,2,2 *read* 1,1,2,2
Page 6, line 17, *after* ("Freon 114 *delete* ", *insert* "),
Page 6, line 38, *for* safetly *read* safely
Page 7, line 118, *for* resuting *read* resulting

THE PATENT OFFICE
19th February, 1979