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INHALATION AEROSOL SUSPENSION OF ANHYDROUS DISODIUM DEXAMETHASONE PHOSPHATE, PROPELLENTS, AND SORBITAN TRIOLEATE

Thomas J. Macek, Glenside, Pa., assignor to Merck & Co., Inc., Rahway, N.J., a corporation of New Jersey

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This application is a continuation-in-part of my earlier filed applications Serial No. 206,159 filed on June 29, 1962, and Serial No. 349,469 filed on March 4, 1964, both now abandoned.

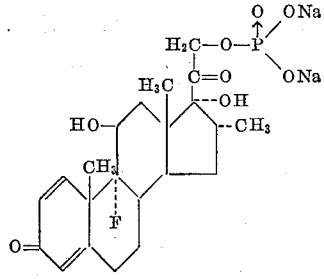
This invention relates to pharmaceutical compositions, and more particularly, to self-propelling, organoleptically-acceptable aerosol compositions containing the water-soluble anti-inflammatory steroid, dexamethasone phosphate.

In many conditions, particularly those which involve the respiratory system as in asthma, bronchitis, infectious and inflammatory diseases of the respiratory tract, and even coughing and the allergic manifestations of the common cold, proper inhalation thereapy would be exceedingly useful. Aerosol application of appropriate and effective medication would also be useful in inflammatory disorders of the nasal mucose such as allergic rhinitis, polyposis, etc.

A recent advance in the mode of administering steroids for asthma, etc. was the development of self-propelling medicament compositions. Up to now, a fully satisfactory inhalation aerosol of an anti-inflammatory steroid has not been made available for general use in medicine. Indeed, the literature even describes some such experimental aerosols as being unacceptable to patients because of their extremely bitter taste, or because they were therapeutically ineffective.

The present invention provides a self-propelling composition of the water soluble steroid dexamethasone phosphate in a dosage of dexamethasone phosphate substantially reduced compared to the usual oral or parenteral dose and in a composition which has an agreeable and acceptable taste.

The water soluble anti-inflammatory steroid, disodium dexamethasone phosphate, employed in the composition of this invention and hereinafter referred to, has the following chemical structure:



It should be substantially anhydrous and finely divided in form for inhalation therapy. The particle size of the dexamethasone phosphate should be between about 1 micron and about 10 microns, and preferably in the range of about 1 to 5 microns. It should constitute from 0.001 to 0.18% of the total composition by weight.

The self-propelling compositions of this invention include substantially anhydrous suspensions or dispersions of the solid dexamethasone phosphate disodium salt medicament uniformly dispersed or suspended throughout the nontoxic liquid propellant with the aid of a suitable dispersing agent. This dispersing agent is sorbitan trioleate (sold as Span 85) and it is employed in the range of 0.01 to 2.0% by weight of the total composition.

The liquified propellant employed in the novel composition of this invention should be non-toxic and have a vapor pressure between about 15 and 70 pounds and preferably between about 20 and 30 pounds per square inch gauge at 70° F. Among the propellants having the above characteristics are the fluorinated or fluorochlorinated lower saturated aliphatic hydrocarbons. The preferred propellants of this type are the halogenated alkanes containing not more than two carbon atoms and at least one fluorine atom. Illustrative of these are trichloromonofluoromethane, dichloromonofluoromethane, monochlorotrifluoromethane, dichlorodifluoromethane, monochlorotrifluoromethane, dichloromonofluoromethane, and 1,2-dichloro-1,1,2,2-tetrafluoroethane. These compounds are available commercially from E. I. du Pont de Nemours and Company under the trade name "Freon," and from others under different trade names.

It will be realized that the fluorinated or fluorochlorinated lower saturated aliphatic hydrocarbons having the above-mentioned characteristics may be employed singularly or in compatible admixtures. In addition, it will be further realized that other non-toxic propellants having a vapor pressure without the limits prescribed above may be utilized in compatible admixtures with or without one or more propellants having the required vapor pressure providing that the vapor pressure of such mixtures is within the prescribed range. This liquefied propellant constitutes substantially the entire remainder of the composition, although other ingredients amounting to as much as 1 to 2% of the total composition by weight may be present.

In preparing the composition of this invention, the dexamethasone phosphate as the disodium salt is first ground, milled or micronized to a particle size in the range specified hereinabove. It is then dried by conventional methods to substantially remove any moisture which may be present. A desired amount of finely divided and substantially anhydrous medicament is then suspended by means of dispersion agitation in a measured amount of the propellant or propellant mixture with the sorbitan trioleate, previously cooled to a temperature of about —25° F. The suspension is made by appropriate dilution, then without permitting the temperature of the suspension to rise above the boiling point of the propellant, the suspension is filled into a suitable container which may be metal, glass or plastic, and the container immediately is sealed with a closure equipped with a suitable dispensing valve arrangement such as described in U.S. Patent 2,721,010. The quantities of the components introduced into the container are calculated to provide the desired concentration of the dexamethasone phosphate in the final composition. Upon warming to room temperature, the contents of the container attain a pressure equivalent to the vapor pressure of the mixture of the propellants employed, which serves as the driving force for the aerosolization.

The following examples illustrate the preparation of specific compositions provided by this invention but it is understood that the invention is not to be restricted thereby to the embodiments described in these examples.

Example 1

	Percent by weight
Dexamethasone phosphate, disodium	0.18
Dichlorodifluoromethane (Freon 12)	34.56
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	65.00
Sorbitan trioleate	0.26
	100.00

Example 2

Dexamethasone phosphate, disodium	0.005
Dichlorodifluoromethane (Freon 12)	34.56
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	65.00
Sorbitan trioleate	0.435
	100.00

Example 3

Dexamethasone phosphate, disodium	0.008
Dichlorodifluoromethane (Freon 12)	34.56
1,2-dichloro-1,2,2-tetrafluoroethane (Freon 114)	65.00
Sorbitan trioleate	0.432
	100.00

Example 4

Dexamethasone phosphate, disodium	0.001
Dichlorodifluoromethane (Freon 12)	34.560
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	63.439
Sorbitan trioleate	2.00
	100.00

When the composition of this invention is utilized for inhalation therapy for asthma and other respiratory diseases there is obtained greater deposition and retention of the medicated particles in that region of the bronchial tree where it is optimally utilized so that a mere fraction of the dose normally required by mouth or by injection need be employed. In addition, the composition is organoleptically-acceptable to the patient. The combined attributes of a reduced dosage, an acceptable taste and an efficient mode of administration enables the composition of the present invention to be utilized by a greater number of patients and over a more prolonged period of time as compared to similar compositions hitherto attempted, described or made available in the art.

The attribute of a reduced dosage is especially important in that this markedly reduces the propensity for the development of other unwanted effects, or side effects, in the patient, as are typical of the administration of a full dose of anti-flammatory steroid over prolonged periods of time. Indeed, clinical experience has shown that use of the present composition by inhalation therapy permits a reduction in total steroid consumption in asthmatics by at least a factor of three and often even by as much as a factor of ten as compared to the usual oral dose. In chronic therapy of diseases such as asthma this becomes exceedingly important. The use of the composition as a nasal aerosol also permits use of the active anti-flammatory steroid in much smaller doses than would be required to produce like effects by oral administration.

What is claimed is:

1. A substantially anhydrous self-propelling dexamethasone phosphate composition suitable for inhalation aerosol therapy and capable of being administered in substantially reduced dosages as compared to other modes of administration consisting essentially of a suspension of substantially anhydrous disodium dexamethasone phosphate having a particle size in the range of from about 1 to 10 microns in a liqui dnontoxic propellent having a vapor pressure between about 15 and 70 pounds per square inch gauge at 70° F. with sorbitan trioleate as a dispersing agent, the ingredients being present within the ranges:

	Percent by weight
Disodium dexamethasone phosphate	0.001 to 0.18
Sorbitan trioleate	0.01 to 2
Propellant	Remainder (substantially)

2. The composition of claim 1 in which said particle size is from about 1 to 5 microns.

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ELBERT L. ROBERTS, *Primary Examiner.*

SHEP K. ROSE, *Assistant Examiner.*