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AEROSOL SOLID MEDICAMENT IN PROPELLANT AND LOW-LEVEL ETHANOL AVOIDING HIGHER-LEVEL ETHANOL DISPERSED-SOLID REFLOCCULATION

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This invention relates to pharmaceutical compositions and more particularly to self-propelling medicament compositions and the method of treatment therewith. This application is a continuation-in-part of my application Serial No. 147,444, filed October 25, 1961, which in turn is a continuation-in-part of Serial No. 112,799, filed May 26, 1961, both now abandoned.

The administration of medicaments by inhalation has been known and employed with varying degrees of success for many years. Usually aqueous solutions of the medicament were atomized by mechanical means and inhaled. Inhalation of medicated steam vapors has been employed. Insufflation of fine powders, again with the aid of mechanical devices, also has been practiced. However, in general, those devices which were effective in reducing the particles of medicament to a size compatible with entry into the bronchial tree were large, cumbersome and could not be employed outside of the home, clinic or hospital. Many of the smaller, portable devices were inefficient or totally ineffective.

The introduction of nebulizers with rubber airbulbs to aspirate the medicament in the lung cavity represented a notable advance in more or less portable devices but their utility was limited because of great variations in pressure obtained depending upon how the device was used. A still further advance was the development of self-propelling medicament compositions such as described in United States Patent No. 2,868,691. Unfortunately, the compositions described therein are not as satisfactory as is desired for inhalation therapy because such compositions do not provide sufficient deposition and retention of the medicated particles where needed to obtain maximum therapeutic effect, namely, on the mucous memberanes of the bronchial tree.

As a result of the aforementioned problems, therapy by inhalation has gone through various cycles of use and disuse and today is not widely practiced. Yet in many conditions, particularly those which involve the respiratory tree, 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 therapy woud be exceedingly useful.

According to the present invention, there are now provided stable self-propelling medicated compositions which have the properties and characteristics which render them highly useful for both inhalation and ophthalmic therapy. The self-propelling compositions of this invention are substantially anhydrous suspensions or dispersions comprised essentially of a solid medicament uniformly dispersed or suspended throughout a substantially anhydrous liquid carrier comprised essentially of a non-toxic propellant and ethanol. These compositions, when prepared employing the above components, described more fully hereinafter, provide an excellent means for administering medicaments in aerosol form for inhalation and ophthalmic therapy. For example, it has been found that when

the compositions of this invention are utilized for inhalation therapy there is obtained greater deposition and retention of the medicated particles in that region of the bronchial tree where it is optimally utilized. As a result of such efficient aerosolization of the medication upon target lung tissue, it is possible in many cases to significantly reduce the dose of the medication employed whereby, with some drugs, such as the anti-inflammatory steroids, a direct benefit accrues to the patient in the elimination of some of the classic side effects of the drug encountered when they are administered over a prolonged period of time by mouth or by parenteral injection.

In addition to the above, it has also been found that by virtue of the efficient aerosolization of the medicament upon the lung tissue, the absorption of many medicaments into the blood stream is greatly enhanced. Accordingly, the compositions of the present invention are also particularly useful for the systemic treatment of various diseases of the body which have heretofore been treated by parenteral administration of antibiotics and other medicaments such as insulin, adrenaline and triodothyronine. Thus, for example, employing insulin as the medicament, diabetes and other diseases which respond to insulin therapy, may be treated by inhalation therapy utilizing the compositions of this invention. The treatment of such diseases by inhalation therapy obviates the need for administering the medicament via the parenteral route which is often discomforting to the patient. Furthermore, the treatment of such diseases by inhalation therapy utilizing the compositions of this invention minimizes or eliminates certain of the classic side effects associated with parenteral administration, particularly intravenous injection.

The self-propelled compositions of the present invention are also particularly useful for ophthalmic therapy. At present, medicaments are normally applied to the eye either in the form of aqueous suspensions or solutions or as ointments. In the former, the medicament is applied by dropper or eye cup whereas with the latter, application is made by pressing a small amount of ointment from a tube around the area of the eyelid which is then mechanically spread by movement of the eye itself. Both methods, however, present considerable problems, especially for self-medication. Thus, for example, accurate positioning is difficult and the application is often wasteful and unsightly. Furthemore, utilizing these methods and compositions, the drug is administered to the eye by direct impact which may give rise to irritation. The self-propelling medicament compositions of this invention, on the other hand, can be self-applied more readily with appreciably less waste of the drug and without leaving any unsightly appearance as is the case with ophthalmic ointments. In addition, the self-propelled compositions of the present invention provide for the administration of the drug to the eye as a fine mist, thereby substantially eliminating the irritation and waste often resulting when the drug is administered by conventional means.

The liquid carrier employed in the novel compositions of this invention is comprised essentially of a mixture of a non-toxic liquid propellant and ethanol. The propellant, which constitutes the major portion of the carrier, should be non-toxic, have a vapor pressure between about 15 and 70 pounds, and preferably between about 35 and 40 pounds per square inch gauge at 70° F., and be completely miscible with ethanol. 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 atoms. Illustrative of these are trichloromonofluoromethane, 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."

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.

The presence of ethanol as a constituent of the liquid carrier is critically essential for the preparation of satisfactory self-propelling medicated compositions contemplated by the present invention. The ethanol, while also serving as additional diluent for the suspended medicated particles, is absolutely essential to prevent agglomeration or settling out of the medicated particles. The discovery that ethanol can be utilized for the prevention of agglomeration or settling out of the medicated particles permits the preparation of stable self-propelling medicated compositions without the necessity of employing other agents, such as surfactants, for this purpose. This represents a decided advancement of the art since it is now possible, for the first time, to prepare stable self-propelling compositions which upon ejection and inhalation thereof permits essentially only the medicament to enter the bronchial tree. This stems from the fact that during the ejection-inhalation cycle, the propellant and ethanol are so rapidly volatilized that very little, if any, enters the bronchial tree. This represents a decided advantage over inhalation compositions containing other agents to prevent agglomeration which, because of their physical properties necessarily reach the desired site of deposition together with the medicament.

The medicaments employed in the compositions of this invention should, of course, be therapeutically suitable for inhalation or ophthalmic therapy as the case may be. In addition, it is critical in order to formulate the compositions of the present invention, that the medicament be a solid at ordinary room temperature, substantially anhydrous in form and virtually insoluble in the liquid carrier employed. Furthermore, it is also critical that the medicament have a particle size of at least about 0.5 to 1 micron and no greater than about 10 microns. Preferably, the particle size of the medicament is such that 95% by weight of the particles are in the range of from about 0.5 to about 4 microns. With these critical requirements in mind, medicaments which can be satisfactorily employed in the self-propelled inhalation and/or ophthalmic compositions of this invention include insulin, triodothyronine and adrenaline; the anti-inflammatory steroids such as hydrocortisone, prednisolone and dexamethasone; antibiotics such as penicillin, neomycin, polymixin, tetracycline, chlortetracycline and oxytetracycline; broncho-dilators such as isoproterenol, phenisonone, epinephrine, phenylephrine and metaraminol; anti-nauseants such as cyclizine, meclizine, pipamazine, dimenhydrinate, trimethobenzamide; analgesics such as ergotamine; antihistamines such as cyproheptadine; antitussives such as noscapine, and mixtures thereof. These medicaments may be employed in their free form or suitable derivatives such as estes, salts and the like may be utilized. It will, of course, be appreciated by those in the art that the selection of the particular form of the medicament employed will be dependent upon its solubility characteristics in the particular carrier system utilized. In addition, it is preferred, but not essential, that the medicament utilized in the preparations intended for inhalation therapy also be water-soluble and for this purpose the form of medicament can be selected accordingly.

It is important that the amount of ethanol employed in the compositions of the present invention be kept at a minimum. Preferably, it should not exceed 5% by weight of the final formulation because higher levels of ethanol may adversely affect the dispersion in that it may cause some reflocculation of the dispersed solids. Desirably, the ethanol is present in an amount of from about 0.5 to about 5.0% and preferably 1.5 to 3.0% by weight of the formulation. In those compositions intended for ophthalmic use, the amount of ethanol preferably should not exceed 3.0%. The concentration of medicament in the self-propelled compositions of the present invention will, of course, vary depending on the medicament and carrier employed as well as the treatment desired. However, in general, the amount of medicament should generally constitute from about 0.02% to about 5% and preferably from about 0.05% to about 1% by weight of the composition, with the propellant constituting the remainder of the composition.

In preparing the compositions of this invention, the medicament is first ground, milled or micronized to a particle size in the range specified hereinabove and then dried by conventional methods to substantially remove any water which may be present. A desired amount of finely divided and substantially anhydrous medicament is then suspended in a measured amount of carrier which has previously been cooled to a temperature of about —25° F. in a suitable container. Without permitting the temperature of the suspension to rise above the boiling point of the propellant, the container which may be metal, glass or plastic is sealed with a closure equipped with a suitable dispensing valve arrangement. The quantities of the components introduced into the container are calculated to provide the desired concentration in the final composition. Upon warming to room temperature, the contents of the container are mixed by agitation of the container.

An alternative and preferred procedure for preparing the compositions of the invention comprises milling a suitable quantity of medicament, which has previously been dried to remove substantially all water, in ethanol, to form a suspension concentrate containing the medicament having the required particle size; subdividing and diluting the thus obtained concentrate in a suitable container with sufficient propellant, previously cooled to about —25° F., to provide the desired concentration of the medicament and ethanol in the final formulation and, without allowing the temperature of the formulation to rise above the boiling point of the propellant, sealing the container with a closure equipped with a suitable dispensing valve arrangement which is preferably metered to dispense an effective dose of the medicament per application or over several applications during a single day. A suitable metered dispensing valve for this purpose is described in United States Patent No. 2,721,010.

Since, in all ophthalmic formulations, sterility must be assured, this factor must be considered. The medicament considered for use in such preparations can be sterilized using ethylene oxide treatment in the conventional manner. The propellant, while not particularly susceptible to bacterial invasion, may, nevertheless, be sterilized by filtration. The containers, previously sterilized by usual procedures, are filled in a sterile area. Once filling is complete, sterility need not be a factor since the pressurized container is never opened.

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

A self-propelling medicament composition suitable for inhalation therapy and containing the following ingredients is prepared as follows:

	Percent by weight
Dexamethasone phosphate, disodium	0.18
Isoproterenol sulfate	0.07
Ethanol (absolute)	1.00
Dichlorodifluoromethane (Freon 12)	34.56
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	64.19
	100.00

13.5 grams of substantially dry dexamethasone phosphate and 5.35 grams of substantially dry isoproterenol sulfate are milled in 75 grams of absolute ethanol to a particle size in the range of from about 0.5 to 10 microns. The resulting suspension concentrate is then subdivided into 500 portions in suitable aerosol containers and each diluted with 14.81 grams of a propellant mixture, previously cooled to about −25° F., containing 35% Freon 12 and 65% Freon 114. Without permitting the temperature of the resulting formulations (which contain 15 grams of material) to rise above the boiling point of the propellant component, the metal containers are then sealed with a closure equipped with a metered valve capable of dispensing the desired amount of medicament per application. Using a metered 70 mg. valve, there will be provided 0.126 mg. of the steroid and 0.049 mg. of the isoproterenol sulfate per application. A regimen of 3 applications four times a day of the formulation is suitable for inhalation therapy.

Example 2

A self-propelled medicament composition suitable for inhalation therapy and containing the following ingredients is prepared as follows:

	Weight, g.
Dexamethasone phosphate, disodium	0.027
Ethanol (absolute)	0.150
Dichlorodifluoromethane (Freon 12)	5.188
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	9.635
	15.000

The medicament, previously dried to remove substantially all water, is milled in ethanol to a particle size such that 95% by weight of the particles are in the range of about 0.5 to 4 microns. The resulting suspension concentrate is placed in a suitable container and diluted with the propellant, previously cooled to about −25° F. Without permitting the temperature of the formulation to rise above the boiling point of the propellant component, the container is sealed with a closure equipped with a metered valve capable of dispensing the desired amount of medicament per application.

Example 3

A self-propelled medicament composition suitable for inhalation therapy and containing the following ingredients is prepared as follows:

	Weight, g.
Dexamethasone phosphate, disodium	0.027
Isoproterenol sulfate	0.011
Ethanol (absolute)	0.300
Dichlorodifluoromethane (Freon 12)	5.132
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	9.530
	15.000

The medicaments, previously dried to remove substantially all water, are milled in ethanol to a particle size in the range of about 0.5 to 10 microns. To the resulting suspension concentrate in a suitable container is then

added the propellants, previously cooled to about −25° F. The remainder of the procedure is the same as in Example 2.

Example 4

A self-propelled medicament composition suitable for ophthalmic therapy and containing the following ingredients is prepared as follows:

	Weight, g.
Dexamethasone phosphate, disodium	0.027
Ethanol (absolute)	0.300
Dichlorodifluoromethane (Freon 12)	5.136
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	9.537
	15.000

The medicament, previously dried and sterilized, is milled in absolute ethanol to a particle size in the range of about 0.5 to 10 microns and the resulting suspension concentrate diluted with the sterile propellant component in a suitable container and the container sealed as described in Example 2.

Example 5

A self-propelled medicament composition suitable for ophthalmic therapy and containing the following ingredients is prepared in accordance with the procedure of Example 4:

	Weight, g.
Prednisolone alcohol	0.050
Ethanol (absolute)	0.150
Dichlorodifluoromethane (Freon 12)	5.18
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	9.62
	15.000

Example 6

A self-propelled medicament composition suitable for inhalation therapy and containing the following ingredients is prepared in accordance with the procedure of Example 2:

	Weight, g.
Epinephrine hydrochloride	0.025
Ethanol (absolute)	0.150
Dichlorodifluoromethane (Freon 12)	5.189
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	9.636
	15.000

Example 7

A self-propelled medicament composition suitable for both inhalation and ophthalmic therapy and containing the following ingredients is prepared in accordance with the procedure of Example 3, except that the medicament, propellant and container are all sterilized prior to use:

	Weight, g.
Prednisolone phosphate	0.100
Ethanol (absolute)	0.450
Dichlorodifluoromethane (Freon 12)	5.058
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	9.392
	15.000

Example 8

A self-propelled medicament composition suitable for inhalation therapy and containing the following ingredi-

ents is prepared in accordance with the procedure of Example 2:

	Weight, g.
Dexamethasone phosphate, disodium	0.027
Isoproterenol sulfate	0.011
Ethanol (absolute)	0.450
Dichlorodifluoromethane (Freon 12)	5.079
1,2 - dichloro - 1,1,2,2 - tetrafluoroethane (Freon 114)	9.433
	15.000

Example 9

A self-propelling medicament composition suitable for inhalation therapy and containing the following ingredients is prepared as follows:

	Weight
Crystalline zinc insulin	400 units (18.2 mg).
Ethanol (absolute)	0.280 g.
Dichlorodifluoromethane (Freon 12)	4.796 g.
1,2 - dichloro - 1,1,2,2-tetrafluoroethane (Freon 114)	8.906 g.

The crystalline zinc insulin, previously dried to remove substantially all water, is milled in ethanol to a particle size range approximating 2 microns. To the resulting suspension concentrate in a suitable container is then added the propellants, previously cooled to about —25° F. The remainder of the procedure is the same as in Example 2. Using a 70 mg. metered valve, there will be provided approximately 2 units of crystalline zinc insulin per increment of metered spray. A regimen of ten sprays per day is suitable for the systemic treatment of diabetes and other diseases which respond to insulin therapy.

Example 10

A self-propelling medicament composition suitable for inhalation therapy and containing the following ingredients is prepared in accordance with the procedure of Example 9:

	Weight, g.
Neomycin sulfate	1.0
Polymixin sulfate	1.0
Ethanol (absolute)	0.7
Dichlorodifluoromethane (Freon 12)	3.95
1,2-dichloro-1,1,2,2-tetrafluoroethane (Freon 114)	7.35

Using a 70 mg. metered valve, each increment of metered spray will provide approximately 5 mg. of each of the antibiotics for inhalation. A regimen of three applications four times a day is suitable for the treatment of chronic bronchitis, allergic bronchitis and similar disorders.

While the foregoing specification has been set forth by way of illustration, it will be understood that various modifications and changes may be made without departing from the spirit and scope of the present invention which is to be limited only by the scope of the appended claims.

I claim:

1. A self-propelling medicament composition consisting essentially of a suspension of a solid, substantially anhydrous medicament in a substantially anhydrous liquid carrier comprised essentially of a mixture of a non-toxic propellant and ethanol, said medicament being substantially insoluble in said mixture of propellant and ethanol and having a particle size in the range of from about 0.5 to about 10 microns, and said ethanol being present in an amount of from about 0.5% to not more than about 5% by weight of said composition, in order to thereby avoid some reflocculation of the dispersed solids caused by higher levels of ethanol.

2. The composition of claim 1 wherein the particle size of the medicament is such that 95% by weight of the particles are in the range of from about 0.5 to about 4 microns.

3. The composition of claim 2 wherein the ethanol is present in an amount of from about 1½ to 3% by weight of said composition.

4. The composition of claim 3 wherein the medicament is dexamethasone disodium phosphate.

5. The composition of claim 3 wherein the medicament is isoproterenol sulfate.

6. The composition of claim 3 wherein the medicament is a mixture of dexamethasone and isoproterenol.

7. A package comprising a pressure-tight container having a valve-controlled opening and containing a self-propelling medicament composition capable of providing a medicament in aerosol form consisting essentially of a suspension of a solid, substantially anhydrous medicament in a substantially anhydrous liquid carrier comprised esentially of a mixture of a non-toxic propellant and ethanol, said medicament being substantially insoluble in said mixture of propellant and ethanol and having a particle size in the range of from about 0.5 to about 10 microns, and said ethanol being present in an amount of from about 0.5% to not more than about 5% by weight of said composition, in order to thereby avoid some reflocculation of the dispersed solids caused by higher levels of ethanol.

8. A method for avoiding some reflocculation of dispersed solids caused by higher levels of ethanol in preparing self-propelled medicament compositions which comprises the steps of drying a solid medicament to remove substantially all water therefrom, reducing said substantially dry medicament to a particle size in the range of from about 0.5 to about 10 microns and suspending said medicament in a substantially anhydrous liquid carrier comprised essentially of a non-toxic propellant and an amount of ethanol sufficient to provide from about 0.5% to not more than about 5% by weight of said composition, thereby forming a suspension wherein said medicament is substantially insoluble in said mixture of propellant and ethanol.

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