United States Patent Office

3,282,781
Patented Nov. 1, 1966

3,282,781

INHALANT COMPOSITIONS

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No Drawing. Filed Nov. 25, 1960, Ser. No. 71,426
16 Claims. (Cl. 167—54)

This invention relates to pharmaceutical compositions and more particularly to self-propelling medicament compositions for inhalation therapy.

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 membranes 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 which involve the respiratory tree, as in asthma, bronchitis, infectious and inflammatory diseases of the respiratory tract, even coughing and the allergic manifestations of the common cold, proper inhalation therapy would 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 inhalation therapy. The self-propelling compositions of this invention are substantially anhydrous, homogeneous solutions comprising in intimate admixture a medicament, a non-toxic liquid propellant, and in certain critical proportions described hereinbelow, a non-toxic organic solvent and a non-toxic hygroscopic glycol. These compositions, when prepared employing the above components described more fully hereinafter, provide an excellent means for administering medicaments in aerosol form for inhalation 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. Still further, it has been found that as a result of such efficient aerosolization of the medication upon target lung tissue, it becomes possible in many cases to significantly reduce the dose of the medication employed. In so doing, 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 as when they are administered

over a prolonged period of time by mouth or by parenteral injection.

The liquid propellant employed in the novel compositions of this invention should be non-toxic and 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. 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 trichloromonofluormethane, 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 organic solvent employed in the compositions of the instant invention must be non-toxic and without undesirable effects on inhalation in the amount present in the aerosol produced. In addition, the solvent should be substantially anhydrous, completely miscible with the propellant or mixture of propellants employed and have a boiling point of less than about 80° C. at normal atmospheric pressure. Examples of solvents which have been found to be particularly satisfactory include the low boiling, non-toxic aliphatic alcohols, such as, for example, ethanol; ethers, such as, for example, ethyl ether and vinyl ether; ketones, such as, for example, acetone; and the halogenated lower alkanes, such as, for example, chloroform. The preferred solvent, however, is ethanol. The above-mentioned solvents may be employed alone or in compatible admixtures. In addition, other solvents or mixtures of solvents which have the properties described above may be utilized.

In addition to the organic solvent, it is essential that the compositions of this invention also contain as an additional component a non-toxic, hygroscopic glycol. It is, of course, necessary that the glycol employed be completely miscible with both the organic solvent and propellant employed. Satisfactory glycols include propylene glycol, triethylene glycol, glycerol, butylene glycol and hexylene glycol. Of these, propylene glycol is preferred.

The presence of the glycol not only serves as an additional solvent but, more important, when employed in the critical portions specified hereinafter permits maximum deposition of the medicated particles in that region of the bronchial tree where it is optimally utilized. Also, because of its hygroscopicity, the presence of the glycol in the composition enables the areosolized medicated particles to grow while in the saturated atmosphere of the lungs, without adversely affecting the desired site of deposition, thereby significantly increasing the total retention of the medicament in the lung cavity.

The medicament employed in the compositions of this invention should be one which is therapeutically effective when administered by inhalation. In addition, the medicament should be soluble in or miscible with the solvent-glycol-propellant medium in an effective amount. Medicaments which can be satisfactorily employed include the adrenocortical steroids, such as hydrocortisone, pred-

nisolone and dexamethasone; bronchodilators, 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 esters, salts and the like may be utilized.

In addition to the above essential components, the compositions of this invention may also contain small amounts of other suitable ingredients such as flavoring agents, sweetening agents, anti-oxidants, stabilizing agents and the like. The latter ingredients are desirably added where the compositions are to be stored for prolonged periods of time.

While the proportions of medicament and propellant may be varied somewhat depending upon the specific medicament and propellant employed, the combined total amount of organic solvent and glycol as well as the ratio or organic solvent to glycol is critical. Thus, it has been found that satisfactory results are obtained when the ratio of organic solvent to glycol is in the range of from about 3:1 to about 5:1 and the total combined amount of these ingredients comprises from about 2% to about 25% by weight of the compositions. Preferably, however, the ratio of organic solvent to glycol is about 3:1 and the total combined amount of organic solvent and glycol comprises from about 10% to about 20% by weight of the composition. The amount of medicament shall generally constitute from about 0.05% to about 5% and preferably from about 0.05% to about 1% by weight of the composition. The amount of propellant employed shall generally constitute at least about 70% and may be as high as about 98% by weight of the composition. Preferably, the propellant component comprises from about 80% to about 90% by weight of the total composition. It will be realized that the amount of propellant component in any given composition essentially makes up the difference between the proportions of medicament, organic solvent, glycol and 100 percent.

In preparing the compositions of this invention, the desired amount of the medicament is dissolved in a measured amount of the solvent-glycol mixture. The resulting solution is then placed into a suitable container which may be metal, glass or plastic. Metal containers are preferably employed when the propelant employed has a vapor pressure in excess of 40 pounds per square inch at 70° F. The open container and contents are then cooled to a temperature of about —25° F. and a measured quantity of the liquified propellant which has also been cooled to about —25° F. is then added and mixed with the solution already present. The quantities of the components introduced into the container are calculated to provide the desired concentration of each in the final composition. Without permitting the temperature of the contents of the container to rise above the boiling point of the propelant, the container is sealed with a closure equipped with a suitable dispensing valve arrangement. Upon warming to room temperature, the contents of the container are mixed by agitation of the container.

An alternative procedure, wherein greater control of moisture contamination may be exercised, is as follows:

A measured amount of medicament is dissolved in a measured amount of the organic solvent-glycol mixture to form a concentrate. The concentrate is added to the container and the container sealed with a closure equipped with a suitable metered value arrangement such as described in U.S. Patent No. 2,721,010. The propellant, under pressure, is then added through the metered valve. The quantity of propellant added is regulated to provide the correct dilution of the final mixture. The contents of the container are then mixed by agitation of the container.

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 containing the following ingredients is prepared as follows:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Ethanol (absolute)	7.5
Propylene glycol	2.5
Dichlorodifluoromethane	89.95
	100

The medicament is dissolved in the solvent-glycol mixture. The resulting solution is placed into a metal container and the open container and contents cooled to about —25° F. The propellant is then cooled to about —25° F., added to the container and mixed with the solution already present. Without permitting the temperature of the contents of the container to rise above the boiling point of the propellant component, the container is sealed with a closure equipped with a suitable dispensing valve arrangement. Upon warming to room temperature, the contents of the container are mixed by agitation of the container.

Example 2

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Ethanol (absolute)	7.5
Propylene glycol	2.5
Dichlorodifluoromethane	31.47
1,2-dichloro-1,1,2,2-tetrafluoroethane	58.48
	100

Example 3

A self-propelling medicament composition containing the following ingredients is prepared as follows:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Saccharin	0.02
Ethanol (absolute)	7.5
Propylene glycol	2.5
Dichlorodifluoromethane	31.48
1,2-dichloro-1,1,2,2-tetrafluoroethane	58.45
	100

The medicament is dissolved in the solvent-glycol mixture. The remaining ingredients with the exception of the propellant are then added. The resulting solution is placed into a metal container and the open container and contents cooled to about —25° F. The remainder of the procedure is the same as in Example 1.

Example 4

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Isoproterenol hydrochloride	0.125
Triethylene glycol	5.0
Ethanol (absolute)	15.0
Dichlorofluoromethane	27.914
1,2-dichloro-1,1,2,2-tetrafluoroethane	51.911
	100

Example 5

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 3:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Isoproterenol hydrochloride	0.125
Saccharin	0.02
Ascorbic acid	0.05
Triethylene glycol	5.0
Ethanol (absolute)	15.0
Dichlorodifluoromethane	27.914
1,2-dichloro-1,1,2,2-tetrafluoroethane	51.841
	100

Example 6

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 3:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Isoproterenol hydrochloride	0.125
Ascorbic acid	0.05
Saccharin	0.02
Propylene glycol	5.00
Ethanol (absolute)	15.00
Dichlorodifluoromethane	27.914
1,2-dichloro-1,1,2,2-tetrafluoroethane	51.841
	100

Example 7

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 3:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Isoproterenol hydrochloride	0.125
Saccharin	0.02
Ascorbic acid	0.05
Hexylene glycol	5.0
Ethanol (absolute)	15.0
Dichlorodifluoromethane	27.914
1,2-dichloro-1,1,2,2-tetrafluoroethane	51.841
	100

Example 8

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Dexamethasone palmitate	0.08
Ethanol (absolute)	1.50
Propylene glycol	.50
Dichlorodifluoromethane	34.27
1,2-dichloro-1,1,2,2-tetrafluoroethane	63.65
	100

Example 9

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 3:

	Percent by weight
Dexamethasone palmitate	0.08
Phenisonone hydrobromide	0.125

Ascorbic acid	0.05
Saccharin	0.02
Ethanol (absolute)	10.0
Propylene glycol	2.5
Dichlorodifluoromethane	30.529
1,2-dichloro-1,1,2,2-tetrafluoroethane	56.696
	100

Example 10

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 3:

	Percent by weight
Dexamethasone tertiary-butylacetate	0.05
Phenisonone hydrobromide	0.125
Ascorbic acid	0.05
Saccharin	0.02
Ethanol (absolute)	12.5
Propylene glycol	2.5
Dichlorodifluoromethane	29.664
1,2-dichloro-1,1,2,2-tetrafluoroethane	55.091
	100

Example 11

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Dimenhydrinate	5.0
Ethanol (absolute)	15.0
Propylene glycol	5.0
Methyl chloride	10.0
Dichlorodifluoromethane	22.75
1,2-dichloro-1,1,2,2-tetrafluoroethane	42.25
	100

Example 12

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Cyclizine	4.0
Ethanol (absolute)	20.0
Propylene glycol	4.0
Trichlorofluoromethane	24.60
Dichlorodifluoromethane	47.40
	100

Example 13

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Dexamethasone palmitate	0.05
Ethanol (absolute)	7.5
1,3-dihydroxybutane	2.5
Dichlorodifluoromethane	31.48
1,2-dichloro-1,1,2,2-tetrafluoroethane	58.47
	100

Example 14

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Dexamethasone palmitate	0.08
Isoproterenol hydrochloride	0.125

	Percent by weight
Propylene glycol	2.5
Ethanol (absolute)	7.5
Dichlorodifluoromethane	31.428
1,2-dichloro-1,1,2,2-tetrafluoroethane	58.367
	100

Example 15

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 3:

	Percent by weight
Dexamethasone tertiary-buylacetate	0.05
Isoproterenol hydrochloride	0.125
Saccharin	0.02
Ascorbic acid	0.05
Propylene glycol	2.5
Ethanol (absolute)	10.0
Dichlorodifluoromethane	30.535
1,2-dichloro-1,1,2,2-tetrafluoroethane	56.720
	100

Example 16

A self-propelling medicament composition containing the following ingredients is prepared according to the process of Example 1:

	Percent by weight
Isoproterenol hydrochloride	0.125
Ethanol (absolute)	10.0
Propylene glycol	2.5
Dichlorodifluoromethane	30.581
1,2-dichloro-1,1,2,2-tetrafluoroethane	56.794
	100

The dexamethasone tertiary-butylacetate and dexamethasone palmitate employed as medicaments in certain of the above examples may be prepared by reacting the corresponding free alcohol with tertiary-butyl acetyl chloride or palmitoyl chloride in the presence of a tertiary amine base such as pyridine employing the process described in United States Patent No. 2,736,734.

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.

What is claimed is:

1. A substantially anhydrous self-propelling medicament composition for inhalation therapy comprising a homogeneous solution of a medicament, a non-toxic propellant, a non-toxic organic solvent and a non-toxic hygroscopic glycol, the ratio of said solvent to said glycol in said composition being from about 3:1 to about 5:1 and the combined amount of organic solvent and glycol comprising from about 2% to about 25% by weight of the composition.

2. A substantially anhydrous self-propelling medicament composition for inhalation therapy comprising a homogeneous solution of a medicament, a non-toxic propellant, a non-toxic organic solvent and a non-toxic hygroscopic glycol, the ratio of said solvent to said glycol in said composition being about 3:1 and the combined amount of organic solvent and glycol comprising from about 10% to about 20% by weight of the composition.

3. A composition as defined by claim **1** wherein the medicament is dexamethasone tertiary-butylacetate.

4. A composition as defined by claim **1** wherein the medicament is isoproterenol hydrochloride.

5. A composition as defined by claim **1** wherein the medicament is dexamethasone palmitate.

6. A composition as defined by claim **1** wherein the medicament comprises a mixture of dexamethasone tertiary-butylacetate and isoproterenol hydrochloride.

7. A composition as defined by claim **1** wherein the medicament comprises a mixture of dexamethasone palmitate and isoproterenol hydrochloride.

8. A composition as defined by claim **1** wherein the medicament comprises a mixture of dexamethasone tertiary-butylacetate and phenisonone hydrobromide.

9. A substantially anhydrous self-propelling medicament composition as defined by claim **1** containing by weight from about 0.05% to about 1.0% dexamethasone tertiary-butylacetate, about 2.5% propylene glycol, from about 7.5% to about 10.0% ethanol, and a non-toxic propellant comprising the remainder of said composition.

10. A substantially anhydrous self-propelling medicament composition as defined by claim **1** containing by weight from about 0.05% to about 1.0% dexamethasone palmitate, about 2.5% propylene glycol, from about 7.5% to about 10.0% ethanol, and a non-toxic propellant comprising the remainder of said composition.

11. A substantially anhydrous self-propelling medicament composition as defined by claim **1** containing by weight from about 0.05% to about 1.0% of a medicament, said medicament comprising a mixture of dexamethasone tertiary-butylacetate and isoproterenol hydrochloride, about 2.5% propylene glycol, from about 7.5% to about 10.0% ethanol, and a non-toxic propellant comprising the remainder of said composition.

12. A substantially anhydrous self-propelling medicament composition as defined by claim **1** containing by weight from about 0.05% to about 1.0% of a medicament, said medicament comprising a mixture of dexamethasone palmitate and isoproterenol hydrochloride, about 2.5% propylene glycol, from about 7.5% to about 10.0% ethanol, and a non-toxic propellant comprising the remainder of said composition.

13. A substantially anhydrous self-propelling medicament composition for inhalation therapy comprising a homogeneous solution of a medicament, said medicament comprising from about 0.05% to about 5% by weight of said composition, a non-toxic organic solvent, a non-toxic hygroscopic glycol, the ratio of said solvent to said glycol in said composition being from about 3:1 to about 5:1 and the combined amount of organic solvent and glycol comprising from about 2% to about 25% by weight of the composition, and a non-toxic propellant, said propellant comprising substantially the remainder of said composition.

14. 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 suitable for inhalation therapy comprising a substantially anhydrous homogeneous solution of a medicament, a non-toxic propellant, a non-toxic organic solvent and a non-toxic hygroscopic glycol, the ratio of said solvent to said glycol in said composition being from about 3:1 to about 5:1 and the combined amount of organic solvent and glycol comprising from about 2% to about 25% by weight of the composition.

15. A substantially anhydrous self-propelling medicament composition for inhalation therapy comprising (1) a homogeneous solution of a sympathomimetic amine, (2) as a non-toxic propellant component, a chlorofluoro lower alkane, (3) ethyl alcohol, as a non-toxic organic solvent, and (4) a polyhydroxyalcohol selected from the group consisting of glycerol and a non-toxic hygroscopic glycol, the ratio of said solvent to said polyhydroxyalcohol in said composition being from about 3:1 to about 5:1 and the combined amount of solvent and polyhydroxyalcohol comprising from about 2 to about 25% by weight of the composition.

16. A substantially anhydrous self-propelling medicament composition for inhalation therapy comprising (1)

a homogeneous solution of a medicament, (2) as a non-toxic propellant component, a chlorofluoro lower alkane, (3) ethyl alcohol, as a non-toxic organic solvent, and (4) a polyhydroxyalcohol selected from the group consisting of glycerol and a non-toxic hygroscopic glycol, the ratio of said solvent to said polyhydroxyalcohol in said composition being from about 3:1 to about 5:1 and the combined amount of solvent and polyhydroxyalcohol comprising from about 2 to about 25% by weight of the composition.

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