United States Patent Office 3,095,355 Patented June 25, 1963

3,095,355

AEROSOL COMPOSITION

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No Drawing. Filed Oct. 12, 1961, Ser. No. 147,402
8 Claims. (Cl. 167—54)

This invention relates to improved self-propelling compositions containing dispersed medicaments for inhalation therapy, and to methods of making and using the same.

It has already been proposed in the art that self-propelling compositions containing medicaments and adaptable to administration of the medicament in aerosol form be employed for inhalation therapy. United States Patent No. 2,868,691, granted January 13, 1959, to Porush et al., describes in detail a number of such medicament containing compositions. In particular, the patent describes self-propelling compositions in which bronchodilator amines and/or their acid-addition salts are dissolved in a non-toxic liquid propellant composition with a liquid co-solvent which assists in dissolving the medicament in the liquefied propellant. According to the patent, the co-solvent constitutes between about 5 percent or 10 percent and 40 percent, preferably between about 20 percent and 40 percent, by weight of the total composition.

A significant disadvantage of such prior art compositions is that the size of the aerosol particle reaching the lungs is too large to permit medically effective distribution of the dissolved drugs, particularly the vasoconstrictors, to those bronchioles of very narrow diameter. In an aerosol composition used for inhalation therapy, it is highly desirable that the aerosol particles have a particle size less than about 10 microns, and preferably less than 3 or 5 microns, such as between 0.5 and 3 microns. With the aerosol-dispersing valves now available in the art, it is not possible to dispense aerosol particles of such fine diameter. Present-day valves, on the contrary, distribute aerosol particles having a diameter of about 35–40 microns. Since these aerosol particles, on leaving the aerosol valve, contain a high proportion of volatile ingredients, i.e. the propellant, the drop size of the aerosol decreases as these volatile materials evaporate, and the size of the particles reaching the lungs is in large part determined by the proportion of non-volatile ingredients in the aerosol composition.

Prior art aerosol compositions, such as those shown in Patent 2,868,691, which contain a large proportion of a relatively involatile co-solvent material such as ethanol, cannot attain by evaporation the desirable small particle size required for maximally effective physiological distribution of the drug in the lungs.

According to the present invention, the small aerosol particle size desired for effective distribution of a medicament in the lungs is obtained by employing self-propelling compositions containing the drugs in micronized form dispersed, rather than dissolved, in a propellant composition. Effective dispersion of the finely divided drug particles in the propellant is accomplished with the use of very small quantities of a suspending agent, present as a coating on the micronized drug particles. Evaporation of the propellant from the aerosol particles after spraying from the aerosol container leaves finely divided drug particles coated with a fine film of the suspending agent. Since the particles themselves are extremely finely divided for incorporation into the aerosol composition, and since the quantity of relatively non-volatile suspending agent employed is very small, the average diameter of the coated particles after evaporation of the volatile propellant therefrom is still quite small and falls easily within the particle size range of less than 10 microns desired for effective distribution of the drug to the bronchioles.

Although many drugs insoluble in typical non-toxic propellant compositions can be dispensed in the manner suggested by the invention, the invention is particularly well-adapted to the dispensing of such antiasthmatic bronchodilator amines as epinephrine and isoproterenol. These materials are generally employed medicinally in the form of water-soluble salts formed by combination of an organic or inorganic acid with these amines. Thus, epinephrine, in its levo or racemic form, can be employed as the chloride, the bitartrate, or the ascorbate, for example. Similarly, isoproterenol may be employed in the form of the sulfate or hydrochloride, etc. These drugs are employed according to the invention in finely divided or "micronized" form in which the average particle size is less than about 5 microns.

The solid drugs are dispersed in a non-toxic propellant composition employing a fatty alcohol as a dispersing agent. In particular, oleyl alcohol, alone or in admixture with other saturated and unsaturated fatty alcohols having 12 to 22 carbon atoms, preferably from 14 to 18 carbon atoms, is employed as the suspending agent.

A minimum quantity of suspending agent sufficient to bring about effective dispersion of the solid drug particles in the propellant composition is employed, and varies with the amount of solid drug to be suspended. For the anti-asthmatic drugs mentioned earlier, minimal quantities of about 0.1 to 0.2 percent by weight of suspending agent, based on the weight of the composition, are employed. Although relatively large amounts of the suspending agent in the self-propelling composition of the invention are not disturbing to the maintenance of dispersion, and are not physiologically harmful, a minimum quantity of dispersing agent is preferably employed since the thickness of the coating of the relatively non-volatile dispersing agent on the micronized drug particles will be determinative of the size of the particles reaching the lungs after evaporation of the volatile propellants therefrom. To maintain an upper particle size limit less than 10 microns, preferably less than 5 microns, quantities of dispersing agent less than about 4 percent by weight of the total composition are suitably employed. Particularly good compositions, from the point of view of particle size, have been obtained using between about 0.5 and about 1 percent by weight of the dispersing agent in the self-propelling composition. It will be seen that this quantity of non-volatile dispersing agent is relatively small compared with even the minimum amount of a co-solvent required in the prior art for solution of a drug in a volatile propellant.

These quantities of suspending or dispersing agent are sufficient for the quantity of drug normally dispersed in a volatile propellant. In general, the drug is dispersed in amounts varying between about 0.1 percent and about 2 percent by weight of the volatile propellant, preferably in amounts varying between 0.15 percent and 0.5 percent by weight of the propellant.

Suitable non-toxic volatile liquid propellants are known in the art, and are discussed in Patent 2,868,691 for example. These materials are generally fluorinated or fluorochlorinated lower saturated aliphatic hydrocarbons, suitably halogenated lower alkanes containing one to four carbon atoms, preferably one or two carbon atoms, and at least one fluorine atom. Any of the materials disclosed in the earlier mentioned patent can be employed in the present invention, including propellants such as dichlorodifluoromethane ("Freon 12"), dichlorotetrafluoroethane ("Freon 114"), and trichloromonofluoromethane ("Freon 11"). These propellants, or suitable mixtures thereof, will produce a propellant vapor

pressure between about 25 and about 60 pounds per square inch at room temperatures (20–25° C.). Suitable mitxures of the propellants can be employed to give a preferred vapor pressure between about 35 and about 40 pounds per square inch at these temperatures. For unknown reasons, the presence of trichloromonofluoromethane ("Freon 11") seems to increase the dispersibility of solid particles in the volatile propellant mixture. However, the vapor pressure of this "Freon" is rather low, and suitable propellant compositions are prepared by mixing other of the "Freons" having higher vapor pressures with "Freon 11." The best propellant compositions contain about 20 percent by weight of "Freon 11," blended with "Freon 12" and/or "Freon 114." A volatile propellant composition containing about 20 percent of "Freon 11," about 30–35 percent by weight of "Freon 114," and between about 45 and 50 percent by weight of "Freon 12" shows particularly good suspending and pressure qualities. However, this mixture and other specific mixtures are not critical to the invention, and any non-toxic liquid volatile propellant such as those earlier described herein may be employed.

Preparation of the self-propelling compositions of the invention proceeds by intimately mixing appropriate quantities of the anti-asthmatic drugs earlier mentioned, preferably in salt form, with oleyl alcohol or mixtures of oleyl alcohol with one or more fatty alcohols having between 12 and 22 carbon atoms, such as lauryl, myristyl, stearyl, cetyl, linoleyl, or behenyl alcohols. It is desired to produce an intimate mixture of the drug and suspending agent in a free flowing form containing a minimum of the suspending agent. In general, this is accomplished by mixing up to 2 parts of the finely divided drug with 1 part of suspending agent, although larger quantities of the drug can be used providing that the drug particles become suitably covered with the suspending agent. Inadequate coverage of the drug particles with the suspending agent is usually indicated by the formation of a very thick, unworkable paste, and if such pastes are formed, additional alcohol is added until a free-flowing composition or slurry is obtained. For complete dispersion, the resulting mixture is usually apssed through a colloid mill. Mixtures with particularly good flow properties contain about 60 percent by weight of suspending agent, the balance being the drug.

The resulting slurry is then metered into aerosol containers, and the non-toxic volatile propellant is then added either by conventional cold fill methods, in which the propellant is chilled to a temperature of about —40° C., or is introduced into the containers at room temperature under pressure. The components of the non-toxic propellant mixture can be added individually or in combination.

Although oleyl alcohol alone is an extremely satisfactory suspending agent, the material is a very mobile fluid. If used in large amounts with a micronized drug, the drug may settle in the pre-mixed drug-alcohol compositions. Such settling might interfere with proper metering of the drug-alcohol mixture into the aerosol containers. In such a case, the other alcohols, which are solids at room temperature, may be added to oleyl alcohol to increase its viscosity. In general, mixtures containing up to equal portions of oleyl alcohol and one or more of the other fatty alcohols mentioned can be employed. Mixtures containing relatively large amounts of the solid alcohols may be viscous or pasty solids at room temperatures, but can be metered well into the dosage containers at slightly elevated temperatures.

The products of the invention are conveniently used in aerosol containers having a metered valve which dispenses a controlled quantity of the self-propelling aerosol composition as a single dose. These containers are well known in the art, and may be made of any materials, such as glass, plastic, or metal adequate to contain the pressures generated by the volatile propellant materials therein.

Conventionally, these metered containers operate by inversion of the container to fill a well of predetermined volume with the self-propelling composition. On activation of the aerosol valve, only this predetermined volume of self-propelling composition is dispersed as an aerosol. Normal handling of an aerosol container, and particularly the manipulation usually performed with a metered aerosol container, causes agitation of container contends sufficient to redisperse any particles which may have settled.

A better understanding of the present invention and of its many advantages can be had by referring to the following examples, given by way of illustration.

Example

A number of free-flowing mixtures containing a micronized drug having a particle size of less than about 5 microns and a fatty alcohol suspending agent were prepared by mixing the following components together in suitable mixing apparatus such as a propeller type-mixer.

Drug and suspending agent:	Parts by weight
(I)	
Epinephrine hydrochloride	2
Oleyl alcohol	3
(II)	
Epinephrine hydrochloride	1
Oleyl alcohol	4
(III)	
Isoproterenol sulfate	2
Oleyl alcohol	3
(IV)	
Isoproterenol sulfate	1
Oleyl alcohol	4
(V)	
Epinephrine hydrochloride	1
Oleyl alcohol	2
Myristyl alcohol	1
(VI)	
Epinephrine hydrochloride	1
Oleyl alcohol	4
Stearyl alcohol	1
(VII)	
Epinephrine hydrochloride	1
Oleyl alcohol	4
Cetyl alcohol	1
(VIII)	
Isoproterenol sulfate	1
Oleyl alcohol	1
Myristyl alcohol	1

These mixtures, hereinafter referred to as "concentrates," were used to formulate self-propelling compositions by admixture with suitably non-toxic volatile liquid propellants in the following proportions:

(A)		
Concentrate	mg—	100
"Freon 12"	gm—	7
"Freon 114"	gm—	7
(B)		
Concentrate	mg—	500
"Freon 12"	gm—	8
"Freon 114"	gm—	4
"Freon 11"	gm—	2
(C)		
Concentrate	mg—	250
"Freon 12"	gm—	7
"Freon 11"	gm—	7

Although specific embodiments have been shown and described herein, it is to be understood that they are illustrative and are not limiting on the scope and spirit of the invention.

What is claimed is:

1. A composition adaptable to use in aerosol form for inhalation therapy and comprising finely divided particles

of a water-soluble acid addition salt of a member of the group consisting of epinephrine and isoproterenol dispersed in a non-toxic liquid propellant, said particles being coated with a dispersing agent selected from the group consisting of oleyl alcohol and mixtures of oleyl alcohol with other fatty alcohols having from 12 to 22 carbon atoms.

2. A composition as in claim 1 wherein said dispersing agent is oleyl alcohol.

3. A composition adaptable to use in aerosol form for inhalation therapy and comprising a liquid non-toxic halogenated lower alkane propellant, about 0.1 to about 2 percent, by weight of said propellant, of finely divided particles of a water-soluble acid addition salt of a member of the group consisting of epinephrine and isoproterenol dispersed in said propellant, and from about 0.1 to about 4 percent, by weight of the composition, of a dispersing agent selected from the group consisting of oleyl alcohol and mixtures of oleyl alcohol with other fatty alcohols having from 12 to 22 carbon atoms, the dispersing agent being present as a coating on said particles.

4. A composition as in claim 3 wherein said dispersing agent is oleyl alcohol.

5. A composition as in claim 3 wherein said propellant composition has a vapor pressure between about 25 and about 60 pounds per square inch at 20°–25° C.

6. A composition as in claim 3 wherein said propellant composition consists essentially of a mixture of dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane.

7. A composition as in claim 3 wherein said water-soluble addition salt is epinephrine hydrochloride.

8. A composition as in claim 3 wherein said water-soluble addition salt is isoproterenol sulfate.

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