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This application is a continuation-in-part of our co-pending application, Serial No. 689,016, filed August 23, 1957, which is in turn a continuation-in-part of our prior application, Serial No. 637,553, filed January 31, 1957, both now abandoned.

This invention relates to self-propelling, power-dispensing compositions capable of dispensing powdered material in aerosol form and to a means for dispensing a dry powder in aerosol form having controlled particle size.

Previously, it has not been possible to provide stable suspensions of powder of substantially uniform particle size in a liquified propellant for use in a pressurized container for aerosol dispensing which would not cause the closure valve, and particularly a metering valve, to stick. It has generally been the practice to prepare self-propelling compositions for aerosol administration by rendering the solid, active ingredient soluble in the liquified propellant by means of a cosolvent. Usually the cosolvent is polar in character, e.g., alcohol. Unfortunately many solids, and particularly certain medicaments, are not stable in polar solvents such as water, or they are rendered unstable when in a polar solvent and in contact with the metal of which the valve of a pressure-tight container is usually constructed. This is the case with epiinephrine. These polar solvent-containing systems may also attack and corrode the metal valve closures of the container and interfere with their functioning. Also, some medicaments and other solids cannot be satisfactorily solubilized in the usual liquified propellants, even though a cosolvent is employed. By means of the present invention it is possible to overcome these shortcomings of the prior art and to provide simple, more stable and more satisfactory aerosol-producing compositions.

It is an object of this invention to provide a package from which a dry powder may be dispensed as an aerosol in a stream of moving gas in a controlled manner or in metered quantities.

It is another object of the present invention to provide stable suspension compositions of powdered solids which may be dispensed consistently in accurate doses through a metering valve for inhalation therapy without causing toxic or irritating side effects on the user.

It is also an object to provide a method for efficiently and effectively dispensing a dry powder in aerosol form of controlled particle size in a manner which avoids sedimentation and particle agglomeration or interference with the functioning of the valve closure and metering mechanisms.

Other objects will be apparent to those skilled in the art from reading the following description.

The self-propelling, powder-dispensing compositions of the invention comprise a finely-divided active solid material or powder suspended in a liquified propellant, in which the solid material is substantially insoluble, and a non-ionic surface-active agent which is liquid at room temperature (65° F.), or ambient temperatures.

The finely divided powder may constitute from about 0.01 to 20% by weight of the total composition. Usually it shall constitute from about 0.05% to 10%, and preferably 0.1 to 3%, by weight of the total composition.

The surface-active agent may constitute from about 0.1 to 20%, desirably between about 0.25 and 5%, and preferably, for medicinal purposes, between about 0.25 and 1%, by weight of the total composition, with the liquified propellant constituting the remainder of the composition. For best results, the concentration of surface-active agent is kept at a minimum as it may tend to solubilize the powder in the propellant, which is undesirable for reasons which will be explained below.

We have discovered that considerable deviation is permissible if the particle size of the powder is small enough. For pharmaceutical purposes the particle size of the powder should desirably be uniform and not greater than 100 microns diameter, since larger particles may tend to agglomerate, separate from the suspension and may clog the valve or orifice of the container. Preferably the particle size should be less than 25 microns in diameter. Desirably the particle size of the finely-divided solid powder should for physiological reasons be less than 25 microns and preferably less than 10 microns in diameter. For best results, the size of the particles of powder should be substantially uniform.

There is no lower limit of particle size except that which is imposed by the use to which the aerosol product is to be put. Where the powder is a solid medicament, the lower limit of particle size is that which will be readily absorbed and retained on or in body tissues. When particles less than one micron in diameter are administered by inhalation they tend to be re-exhaled by the patient.

Desirably the finely-divided powder should be substantially insoluble in each of the liquified propellant, the surface-active agent and in a liquified propellant-surface-active mixture. In the majority of cases we find that solid compounds which are predominantly polar in nature by reason of a sufficient number of polar substituent groups such as hydroxyl, amino and carboxyl groups, and salts thereof, provide most satisfactory compositions in accordance with the invention. If the powder is substantially soluble, crystal growth may occur and the particle size of the aerosolized powder when dispensed cannot be controlled. Since the compositions of the invention are intended to be used for dispensing powders in aerosol form by operating the valve of a pressure-tight container charged with the compositions, it is desirable that the particle size of the suspended powder be regulated and agglomeration reduced. It is clear that if agglomeration of the powder takes place, it may tend to clog the narrow valve orifice and render the dispensing device inoperative, or if a metering valve is employed, it may be rendered inaccurate. This may lead to inaccurate dosages, which in the case of highly toxic chemicals may lead to undesirable results. In addition to increasing the particle size and clogging orifices, agglomeration may...
make the suspension unstable and of unsuitable appearance. In the case of powdered medicinals, adsorption in the body may be made ineffective. Consequently, it is desirable that the finely-divided powder materials be insoluble in the other components of the compositions.

Where a finely-divided powder, such as a medicament, tends to be somewhat soluble in the mixture of surface-active agent and liquefied propellant, it is sometimes possible to overcome this difficulty by employing a less soluble form of the powder. For example, instead of employing basic phenylephrine, its hydrochloride may be employed. Also, different liquefied propellants may be employed in which the powder is less soluble.

Illustrative of the versatility of the compositions of the invention is the fact that the solid components may be in a morpous or crystalline nature. We prefer to use crystalline materials, as is indicated by the specific examples given below. Early efforts to produce self-propelling powder dispensing compositions showed that even to obtain compositions having only borderline properties, it was necessary to limit the solid materials employed to amorphous materials.

As will be apparent to those skilled in the art, one of the advantages of the compositions of the present invention is that they do not require the presence of a polar solvent, such as water. The compositions may be substantially anhydrous.

However, in the present invention, especially where water-soluble medicaments are employed, we have discovered that moisture control is important at all stages of processing. We have found that the total moisture content for finely-dispersed water-soluble medicaments should be less than 300 parts per million by weight of total composition. This moisture control has been found to be critical to ensure the stability of the suspension during periods of storage. For instance, in the case of Example 10 hereinbelow, when more than 300 parts per million of water are present, the medicament agglomerates within one month at room temperature and deposits on the walls of the container. This adversely affects the dose delivered, in addition to resulting in a pharmaceutically inelegant preparation. Another means of controlling and reducing the moisture content of the composition is to introduce before closing the container in which the composition is packaged, small fragments of an anhydrous, nonreactive desiccant, such as silica gel or calcium sulfate. This reduces the moisture content of the liquid phase of the composition below that which causes agglomeration. Usually 100 mgm. of desiccant is sufficient for a 10 ml. container charged with composition.

The solid active component to be aerosolized may be a medicament, such as a vasoconstrictive amine or its acid-addition salts, a hormone, enzyme, alkaloide, steroid, analgesic, bronchodilator, antihistamine, antitiussive, analgesic, bronchodilator, antihistamine, antitiussive, anti-inflammatory, antibacterial, and surfactant compositions of these. Examples of the medicaments which may be employed are: isoproterenol (alpha (isopropylaminoethyl)propanecyclohexanol) hydrochloride or sulfate, phenylephrine, phenylpropanolamine, glucagon, adrenochrome, trypsin, epinephrine, ephedrine, nortriptyline, codeine, atropine, morphine, dihydrocodeine, amygdalin, methyprynine, cyano-

The liquefied 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. Substantially involatile liquids are also employed in the other components of the compositions.

The preferred halogenated lower alkane compounds may be represented generally by the formula CmH2mF2, wherein m is an integer less than 3, n is an integer or zero, y is an integer or zero, and z is an integer, such as n+y=2x2z+2. Examples of these propellants include: difluoromethane ("Freon 12"), dichlorotetrafluoroethane ("Freon 114") CCl2F2,CClF2, trichloromonofluoromethane ("Freon 11"), dichloromonofluoromethane ("Freon 21"), monochlorodifluoromethane ("Freon 22"), trichlorotrifluoromethane ("Freon 113"), and monochlorotrifluoromethane ("Freon 133"). Pressure/vapor pressure characteristics may be obtained by using certain mixtures of these compounds, e.g., "Freon 11" with "Freon 12" or "Freon 12" with "Freon 14."

For example, dichlorodifluoromethane, which has a vapor pressure of about 70 pounds per square inch gauge and 1,2-dichloro-

various uses including for dental applications, where 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. Usually the active medicament component may also be a cosmetic substance such as talc, an antiperspirant such as aluminum chloride, etc.; a polishing material such as jeweler's rouge; a dye, such as the approved food colorings; a lubricant, such as graphite and other finely-divided materials; as well as other useful substances.

While we do not wish to be bound by any theory to explain the excellent results which are obtained with the compositions of the invention, evidence available to date indicates that the surface-active agent acts by forming a
surface coating, which may even be a mono-molecular film or layer, on the finely-divided powder which prevents the particles from agglomerating either when dispersed in the propellant or when in the valve of the container.

After an extensive investigation employing many surface-active agents it was discovered that particular agents or combinations of them are required to give desirable results. During this investigation it was found unexpectedly that a number of surface-active agents provided poor suspensions and failed to prevent agglomeration.

The liquid, non-ionic, surface-active agent employed should have a 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 lipophile 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.

Surface-active agents which are solids at room temperature have been tried but appear to be unacceptable generally due to clogging of the valve and adapter orifices on delivery. Lubricants for the valve, such as calcium stearate, which is without surfactant properties, were not found to be satisfactory, because they do not help to keep the powdered medicament uniformly dispersed in the propellant.

Those surface-active agents which are soluble or dispersible in the propellant are effective. The more propellant-soluble surface-active agents are the most effective.

For medicinal use it is also important that the surface-active agent should be non-irritating and safe to the 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 capric, octolic, lauric, palmitic, stearic, linoleic, linolenic, oleic and oleic acids with an aliphatic polyhydric alcohol or similar example, ethylene glycol, glycerol, erythritol, arabitol, mannitol, sorbitol, the hexitol anhydrides derived from sorbitol (the sorbitan esters sold under the trademark "Span") 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 monoleate) 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

Indicative of the specificity of the surface-active agent in the compositions of the invention, there is reported below the results obtained with surface-active agents falling outside of the scope of the present invention and certain lubricants. These results are based upon tests employing the surface-active agent or lubricant in a concentration of 0.5% with a suspension of 0.5% of hydrocortisone acetate in a "Freon" mixture consisting of 30% "Freon 11" and 70% of a mixture containing 61.5% "Freon 114" and 38.5% "Freon 12." Hydrocortisone acetate was used because it is one of the more easily suspended materials.

<table>
<thead>
<tr>
<th>Compound Tested</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraffin Wax</td>
<td>Deposits as a solid in the adapter leading from the discharge valve and impairs delivery. Non-homogenous. Lubricates valve.</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>Same as for paraffin wax.</td>
</tr>
<tr>
<td>Steryl Alcohol (solid)</td>
<td>Same as for paraffin wax.</td>
</tr>
<tr>
<td>Glycerol</td>
<td>Same as for paraffin wax.</td>
</tr>
<tr>
<td>Petroleum</td>
<td>Petroleum suspends in &quot;Freon.&quot;</td>
</tr>
<tr>
<td>Oleyl Alcohol (liquid)</td>
<td>Poor emulsion, but separates rapidly. Sticks to sides of container. Lubricates valve.</td>
</tr>
<tr>
<td>Polyethylene Glycol 300</td>
<td>Poor suspension, not very homogeneous, separates quite rapidly, lubricates valve.</td>
</tr>
<tr>
<td>Mineral Oil</td>
<td>Immiscible with &quot;Freon.&quot;</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>Poor suspension, clumpy, breaks rapidly, lubricates valve.</td>
</tr>
<tr>
<td>&quot;MYRJ 41&quot; (Polyoxyethylene stearate)</td>
<td>Poor suspension, but not suitable as homogenous; causes sticking of discharge valve.</td>
</tr>
<tr>
<td>&quot;JRJ 30&quot; (Polyoxyethylene lauryl alcohol)</td>
<td>Very good suspension, clumpy, sticks to container, breaks very rapidly, lubricates valve.</td>
</tr>
<tr>
<td>&quot;ΤΕΕΟ Α1&quot; (Polyoxyethylene sorbitan mono-oleate)</td>
<td>Very poor suspension, clumpy, lubricates valve.</td>
</tr>
</tbody>
</table>

We have further discovered that in the case of compositions of the invention employing certain finely-divided powders there is a tendency to form a layer of the propellant in the container and that these layers tend to deposit or "cake" powdered material on the container walls above the liquid level. This has been found to occur only with those powders which have a specific gravity less than that of the propellant.

This tendency to deposit or "cake out" is a serious disadvantage in that (1) such powder deposited on the container walls is not dispensed from the container, (2) the dose delivered is not correct and becomes progressively less as the amount left in the container becomes smaller and (3) in a transparent container the appearance of the product is impaired. The greater the difference in specific gravity between the powder and the propellant, the more pronounced in this tendency. By means of the present invention, it is possible to overcome these drawbacks and to provide more stable, uniform, attractive and satisfactory aerosol-producing compositions.

In some cases the undesirable deposition or caking which results where the specific gravity of the finely divided powder is substantially less than that of the propellant can be overcome by lowering the specific gravity of the liquid phase, for example by using a propellant of lower specific gravity, such as butane, or by increasing the specific gravity of the solid active powder component, for example in the case of phenylephrine by using the bitartrate salt instead of hydrochloride. In many cases, however, it is not possible to find a suitable alternative form of the active material. In such cases we have discovered, surprisingly, that the introduction of a sufficient quantity of an additional auxiliary finely divided solid of density greater than that of the liquid phase, will prevent the surface spread of lighter powders, thus avoiding "caking out" and the associated, above-mentioned drawbacks.

The nature of such an auxiliary solid may be of any chemical type, provided that it is compatible with the other ingredients and insoluble in the propellant. For example, we may use an inorganic compound such as sodium sulfate, calcium chloride or sodium chloride. We may also use an organic material such as powdered lactose, sucrose, epinephrine bitartrate, nonamin sulfonate, or graphite. The auxiliary solid, when used in medicinal and cosmetic preparations, should be non-toxic and non-irritant. In all cases it should be without deleterious effect on the properties of the dispensed product or on the user. The particle size of the auxiliary solid should
be of the same order of magnitude as the active ingredients. The auxiliary powder may also function as a desiccant for the self-propelling compositions as in the case of anhydrous sodium sulfate or calcium chloride or a clinically active component in the case of a medicinal preparation. Such clinically active component is illustrated by neomycin sulfate and epinephrine bitartrate.

We have discovered that the quantity of the auxiliary powder which is employed shall desirable fall within certain limits. This amount will be discussed below.

If the following symbols have the meaning given:

$\rho_A =$ sp. gr. of auxiliary solid
$\rho_p =$ sp. gr. of propellant
$\rho_{q,p} =$ sp. gr. of total powder constituents (auxiliary solid and active constituent)
$\sigma =$ wt. gr. of active constituent
$\sigma = $ wt. of auxiliary solids
$p =$ wt. of propellant
$q =$ wt. of total powder constituents
$u =$ wt. of active constituent

It is apparent that $q = u + l + a$ (1)

To prevent surface deposit or caking the following condition must exist:

$p_q$ minus $p_p$ must not be less than zero (2)

This condition is satisfied when:

$p_\rho =$ equal to or greater than $p_p$ (3)

thus when $q$ equals $u$, $a$ equals zero. But when $p_\rho$ is less than $p_p$, the following exists:

$p_\rho = \frac{u + a}{u + a + p}$

or

$p_\rho = \frac{u + a}{u + a + p}$

For a theoretical minimum, condition 2 becomes:

$p_\rho$ minus $p_p$ = zero OR $p_{q,p}$ = $p_p$

Applying this information to Equation 4, then:

$\frac{u + a}{u + a + p}$

thus:

In terms of the above defined symbols, when $p_\rho$ is equal to or greater than $p_p$, a satisfactory composition is obtained whereby no surface deposit or caking of powder is obtained without the employment of an auxiliary solid or powder. When $p_\rho$ is less than $p_p$, the minimum amount of auxiliary solid required to prevent deposit of solid from the composition, is expressed by Equation 5 above. We have found that satisfactory results may be obtained when up to about ten times the minimum is employed, but we prefer to employ between $\sigma_{\text{min}}$ and three times $\sigma_{\text{min}}$.

The compositions of the invention may be used to apply measured amounts of aerosolized solid medicaments into body cavities such as the throat or nose. They also provide a means of producing aerosolized medicaments suitable for inhalation therapy. Inhalation therapy is prompt through the immediate contact with the blood through the alveolar membrane. It also enables drugs to act at respiratory sites with respiratory efficiency. Undesirable systemic effects as happens often when drugs are administered by other routes. With very volatile substances inhalation approaches intravenous therapy in rapidity of action. It will often avoid the necessity of parenteral injections. Previously aerosols for this purpose have been prepared by nebulizing aqueous solutions, for example penicillin solutions in the treatment of pneumonia. Suspensions in oil have been suggested in the treatment of bronchial asthma, but this is now widely condemned by the medical profession.

In producing the compositions and packages of the invention, a container equipped with a valve is filled with a propellant containing the finely-divided powder in suspension. A container may first be charged with a weighed amount of dry powder which has been ground to a predetermined particle size, or in a slurry of powder in the cooled liquid propellant. Alternatively and preferably, the powder and the surface-active agent may be triturated or homogenized first into a uniform paste, for instance, by a pestle and mortar. This paste is then dispersed in the cooled liquid propellant. This procedure fosters uniform wetting of the powder particles. A composition may also be filled by introducing powder and propellant by the normal cold 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 an aerosol of dry powder. Throughout the preparation of the product care is desirably exercised to minimize the absorption of moisture where the powder is water-soluble. This may be accomplished by operating in a dehumidified atmosphere using only dry materials and equipment.

When it is necessary to employ an auxiliary solid or powder to prevent surface deposit or caking, it is desirably introduced into the composition at the time that powdered active solids are introduced. This process has been employed in Examples 20 through 30 below. Alternatively, the auxiliary solid can be added to the composition after prewetting it with the surface-active agent or propellant.

In order more clearly to disclose the nature of the present invention, the following examples illustrating compositions in accordance with the invention will now be described. It should be understood, however, that this is done solely by way of example and is intended neither to delineate the scope of the invention nor limit the ambit of the appended claims. In the examples which follow, the process described above was employed. In the examples which follow and throughout the specification, the quantities of material are expressed in terms of percentages by weight of the total composition, unless otherwise specified. The range of particle size specified in each example is that existing at the time of formulation. Where a constituent is described as "micronized," it comprises 90% by weight of particles having a particle size range of between 1 and 5 microns. Examples 20 through 30 illustrate compositions in accordance with the invention employing an auxiliary solid to prevent surface deposit or caking.

Example 1

<table>
<thead>
<tr>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 3 microns)</td>
</tr>
<tr>
<td>&quot;Span 85&quot; (sorbitan trioleate)</td>
</tr>
<tr>
<td>&quot;Freon 11&quot; (trichloromonofluoromethane)</td>
</tr>
<tr>
<td>&quot;Freon 114&quot; (dichlorotetrafluoroethane)</td>
</tr>
<tr>
<td>&quot;Freon 12&quot; (dichlorodifluoromethane)</td>
</tr>
<tr>
<td>100.0</td>
</tr>
</tbody>
</table>

Example 2

<table>
<thead>
<tr>
<th>Gm.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trypsin, amorphous (more than 90% by weight within the particle size range of 1 to 10 microns)</td>
</tr>
<tr>
<td>&quot;Span 85&quot; (sorbitan trioleate)</td>
</tr>
<tr>
<td>Propellant A</td>
</tr>
</tbody>
</table>
### Example 3

| Prednisolone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.5 |
| "Span 85" (sorbitan trioleate) | 0.5 |
| "Propellant B" | 99.0 |
| **Total** | **100.0** |

| Prednisolone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 10.0 |
| "Freon 11" (trichloromono-fluoromethane) | 50.4 |
| "Freon W" (as defined in Example 2) | 31.6 |
| Butane | 8.0 |
| **Total** | **100.0** |

### Example 4

| ACTH (adrenocorticotropic) (amorphous) (10 USP units/mg) (more than 90% by weight within the particle size range of 1 to 20 microns) | 1.00 |
| "Span 85" (sorbitan trioleate) | 0.25 |
| "Freon 11" (trichloromono-fluoromethane) | 5.00 |
| "Freon W" (as defined in Example 2) | 99.75 |
| **Total** | **100.0** |

### Example 5

| Insulin, amorphous (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.25 |
| "Span 85" (sorbitan trioleate) | 0.25 |
| "Freon W" (as defined in Example 2) | 99.50 |
| **Total** | **100.0** |

### Example 6

| Epinephrine, crystalline (free base) (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.28 |
| "Span 85" (sorbitan trioleate) | 0.25 |
| "Freon 11" (trichloromono-fluoromethane) | 5.00 |
| "Freon W" (as defined in Example 2) | 94.47 |
| **Total** | **100.0** |

### Example 7

| Epinephrine bitartrate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.50 |
| "Span 85" (sorbitan trioleate) | 0.50 |
| "Freon 11" (trichloromono-fluoromethane) | 49.50 |
| "Freon 12" (dichlorodifluoromethane) | 49.50 |
| **Total** | **100.0** |

### Example 9

| Isopropylterenol hydrochloride, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.25 |
| "Span 85" (sorbitan trioleate) | 0.25 |
| "Freon 11" (trichloromono-fluoromethane) | 49.75 |
| "Freon 12" (dichlorodifluoromethane) | 49.75 |
| **Total** | **100.00** |

### Example 10

| Phenylephrine hydrochloride, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.25 |
| Neomycin sulfate | 0.11 |
| Hydrocortisone | 0.04 |
| "Span 85" (sorbitan trioleate) | 0.25 |
| "Freon 11" (trichloromono-fluoromethane) | 49.675 |
| "Freon 12" (dichlorodifluoromethane) | 49.675 |
| **Total** | **100.00** |

### Example 11

| Neomycin sulfate, crystalline (more than 90% by weight within the particle size range of 1 to 25 microns) | 0.50 |
| "Span 85" (sorbitan trioleate) | 0.25 |
| "Freon 11" (trichloromono-fluoromethane) | 4.75 |
| "Freon W" (as defined by Example 2) | 94.50 |
| **Total** | **100.00** |

### Example 12

| Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.50 |
| "Surfactant G-1087" (polyoxyethylene sorbitol hexaoctolate) | 0.50 |
| "Propellant C" | 99.00 |
| **Total** | **100.00** |

### Example 13

| Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.50 |
| "Ariacel C" (sorbitan sesquioleate) | 0.50 |
| "Propellant C" (as defined by Example 12) | 99.00 |
| **Total** | **100.00** |

### Example 14

| Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.50 |
| "Span 80" (sorbitan monooleate) | 0.50 |
| "Propellant C" (as defined by Example 12) | 99.00 |
| **Total** | **100.00** |

### Example 15

| Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) | 0.50 |
| "Span 85" (sorbitan trioleate) | 0.50 |
| "Propellant C" (as defined by Example 12) | 99.00 |
| **Total** | **100.00** |
### Example 11
Narcotine, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) ........................................ 3,014,844
“Span 85” (sorbitan trioleate) .................................................. 10.00
“Freon W” (as defined by Example 2) ........................................ 89.00

**Total** ........................................................................... 100.00

### Example 12
Phenylephrine hydrochloride (crystalline), micronized ........................................ 3,016,844
Epinephrine bitartrate (crystalline), micronized ........................................ 0.25
“Span 85” (sorbitan trioleate) .................................................................. 1.0
Propellant S (as defined in Example 20) ........................................ 98.0

**Total** ........................................................................... 100.00

### Example 13
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Sucrose (crystalline), powdered .................................................................. 0.50
“Span 85” (sorbitan trioleate) .................................................................. 0.75
Propellant S (as defined in Example 20) ........................................ 98.5

**Total** ........................................................................... 100.00

### Example 14
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
“Span 85” (sorbitan trioleate) .................................................................. 1.0
Propellant S (as defined by Example 20) ........................................ 98.0

**Total** ........................................................................... 100.00

### Example 15
Iron oxide (jeweler’s rouge) (more than 90% by weight within the particle size range of 1 to 5 microns) ........................................ 1.0
“Span 80” (sorbitan monooleate) ....................................................... 0.25
“Freon 12” (dichlorodifluoromethane) .................................................. 98.75

**Total** ........................................................................... 100.00

This composition is useful for polishing optical components.

### Example 16
Hydrocortisone acetate, crystalline (more than 90% by weight within the particle size range of 1 to 5 microns) ........................................ 0.5
Olive oil ....................................................................................... 0.5
“Freon 111” (trichloromonofluoromethane) ........................................ 30.0
“Freon W” (as defined by Example 2) ........................................ 69.0

**Total** ........................................................................... 100.0

### Example 17
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Phenylpropanolamine hydrochloride (crystalline), micronized ......................... 0.50
Neomycin sulfate (crystalline), micronized ................................................. 0.10
Hydrocortisone (crystalline), micronized .................................................. 0.04
Sodium sulfate (anhydrous), micronized .................................................. 0.35
“Span 85” (sorbitan trioleate) .................................................................. 0.80
Propellant S ..................................................................................... 97.96

**Propellant S consists of:**  
“Freon 12” (dichlorodifluoromethane) .................................................. 27  
“Freon 11” (trichloromonofluoromethane) .............................................. 30  
“Freon 114” (dichlorotrifluoroethane) ................................................... 43

**Total** ........................................................................... 100.00

### Example 18
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Phenylpropanolamine hydrochloride (crystalline) ........................................... 0.50
Neomycin sulfate (crystalline), micronized ................................................. 0.10
Hydrocortisone (crystalline), micronized .................................................. 0.04
Sodium sulfate (anhydrous), micronized .................................................. 0.35
“Span 85” (sorbitan trioleate) .................................................................. 0.80
Propellant S ..................................................................................... 97.96

**Propellant S consists of:**  
“Freon 12” (dichlorodifluoromethane) .................................................. 27  
“Freon 11” (trichloromonofluoromethane) .............................................. 30  
“Freon 114” (dichlorotrifluoroethane) ................................................... 43

**Total** ........................................................................... 100.00

### Example 19
Propellant S (as defined by Example 20) ........................................ 98.5

**Total** ........................................................................... 100.00

### Example 20
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Phenylpropanolamine hydrochloride (crystalline) ........................................... 0.50
Neomycin sulfate (crystalline), micronized ................................................. 0.10
Hydrocortisone (crystalline), micronized .................................................. 0.04
Sodium sulfate (anhydrous), micronized .................................................. 0.35
“Span 85” (sorbitan trioleate) .................................................................. 0.80
Propellant S ..................................................................................... 97.96

**Propellant S consists of:**  
“Freon 12” (dichlorodifluoromethane) .................................................. 27  
“Freon 11” (trichloromonofluoromethane) .............................................. 30  
“Freon 114” (dichlorotrifluoroethane) ................................................... 43

**Total** ........................................................................... 100.00

### Example 21
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Phenylpropanolamine hydrochloride (crystalline) ........................................... 0.50
Neomycin sulfate (crystalline), micronized ................................................. 0.10
Hydrocortisone (crystalline), micronized .................................................. 0.04
Calcium chloride, micronized ................................................................. 0.10
“Span 85” (sorbitan trioleate) .................................................................. 0.50
Propellant S (as defined by Example 20) ........................................ 99.01

**Total** ........................................................................... 100.00

### Example 22
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Sodium chloride (crystalline), powdered ................................................... 0.50
“Span 85” (sorbitan trioleate) .................................................................. 0.75
Propellant S (as defined in Example 20) ........................................ 98.5

**Total** ........................................................................... 100.00

### Example 23
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
“Span 85” (sorbitan trioleate) .................................................................. 1.0
Propellant S (as defined in Example 20) ........................................ 98.0

**Total** ........................................................................... 100.00

### Example 24
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
“Span 85” (sorbitan trioleate) .................................................................. 1.0
Propellant S (as defined by Example 20) ........................................ 98.5

**Total** ........................................................................... 100.00

### Example 25
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Neomycin sulfate (crystalline), micronized ................................................. 3.0
“Span 85” (sorbitan trioleate) .................................................................. 1.0
Propellant S (as defined by Example 20) ........................................ 95.0

**Total** ........................................................................... 100.00

### Example 26
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Graphite powder .................................................................................. 0.25
“Span 85” (sorbitan trioleate) .................................................................. 0.50
Propellant S (as defined by Example 20) ........................................ 99.0

**Total** ........................................................................... 100.00

### Example 27
Hydrocortisone acetate (crystalline), micronized ........................................... 0.88
Sodium sulfate (anhydrous), micronized .................................................. 0.88
“Span 85” (sorbitan trioleate) .................................................................. 1.00
Propellant S–2 ..................................................................................... 97.24

**Propellant S–2 consists of:**  
“Freon 12” (dichlorodifluoromethane) .................................................. 50  
“Freon 11” (trichloromonofluoromethane) .............................................. 25  
“Freon 114” (dichlorotrifluoroethane) ................................................... 25

**Total** ........................................................................... 100.00

### Example 28
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Lactose, powdered .................................................................................. 0.50
“Span 85” (sorbitan trioleate) .................................................................. 0.75
Propellant S (as defined by Example 20) ........................................ 98.5

**Total** ........................................................................... 100.00

### Example 29
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Neomycin sulfate (crystalline), micronized ................................................. 0.08
“Span 85” (sorbitan trioleate) .................................................................. 0.50
Propellant X ....................................................................................... 99.07

**Propellant X consists of:**  
“Freon 12” (dichlorodifluoromethane) .................................................. 30  
“Freon 11” (trichloromonofluoromethane) .............................................. 30  
“Freon 114” (dichlorotrifluoroethane) ................................................... 40

**Total** ........................................................................... 100.00

### Example 30
Phenylephrine hydrochloride (crystalline), micronized ........................................ 0.25
Neomycin sulfate (crystalline), micronized ................................................. 0.08
Propellant S (as defined by Example 20) ........................................ 98.5

**Total** ........................................................................... 100.00

### Example 31
Sodium sulfate (crystalline), micronized .................................................... 0.15
Example 31

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Span 85&quot; (sorbitan trioleate)</td>
<td>0.70</td>
</tr>
<tr>
<td>Propellant X (as defined by Example 29)</td>
<td>98.62</td>
</tr>
</tbody>
</table>

Example 32

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylpropanolamine hydrochloride, crystalline, micronized</td>
<td>0.49</td>
</tr>
<tr>
<td>Phenylephrine hydrochloride, crystalline, micronized</td>
<td>0.35</td>
</tr>
<tr>
<td>Neomycin sulfate, crystalline, micronized</td>
<td>0.10</td>
</tr>
<tr>
<td>Hydrocortisone, crystalline, micronized</td>
<td>0.04</td>
</tr>
<tr>
<td>Sodium sulfate, crystalline (anhydrous), micronized</td>
<td>0.35</td>
</tr>
<tr>
<td>&quot;Span 85&quot;</td>
<td>0.47</td>
</tr>
<tr>
<td>&quot;Freon 113&quot;</td>
<td>1.00</td>
</tr>
<tr>
<td>&quot;Freon 11&quot;</td>
<td>1.00</td>
</tr>
<tr>
<td>&quot;Freon 12&quot;</td>
<td>29.02</td>
</tr>
<tr>
<td>&quot;Freon 114&quot;</td>
<td>38.71</td>
</tr>
</tbody>
</table>

Example 33

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine hydrochloride, crystalline, micronized</td>
<td>0.25</td>
</tr>
<tr>
<td>Phenylpropanolamine hydrochloride, crystalline, micronized</td>
<td>0.50</td>
</tr>
<tr>
<td>Neomycin sulfate, crystalline, micronized</td>
<td>0.08</td>
</tr>
<tr>
<td>Methapyrilene hydrochloride, crystalline, micronized</td>
<td>0.10</td>
</tr>
<tr>
<td>Sodium sulfate, crystalline, micronized</td>
<td>0.35</td>
</tr>
<tr>
<td>&quot;Span 85&quot;</td>
<td>0.46</td>
</tr>
<tr>
<td>&quot;Freon 113&quot;</td>
<td>1.00</td>
</tr>
<tr>
<td>&quot;Freon 11&quot;</td>
<td>29.01</td>
</tr>
<tr>
<td>&quot;Freon 114&quot;</td>
<td>38.70</td>
</tr>
<tr>
<td>&quot;Freon 12&quot;</td>
<td>29.01</td>
</tr>
</tbody>
</table>

Example 34

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalline glucagon, micronized</td>
<td>0.156</td>
</tr>
<tr>
<td>&quot;Span 85&quot;</td>
<td>0.468</td>
</tr>
<tr>
<td>&quot;Propellant S&quot; (as defined by Example 20)</td>
<td>99.376</td>
</tr>
</tbody>
</table>

Example 35

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous cyanocobalamin, crystalline, micronized</td>
<td>0.039</td>
</tr>
<tr>
<td>&quot;Span 85&quot;</td>
<td>0.250</td>
</tr>
<tr>
<td>&quot;Propellant S&quot; (as defined by Example 20)</td>
<td>99.711</td>
</tr>
</tbody>
</table>

Example 36

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorotetracycline hydrochloride, crystalline, micronized</td>
<td>0.5</td>
</tr>
<tr>
<td>Lactose</td>
<td>0.5</td>
</tr>
<tr>
<td>&quot;Span 85&quot;</td>
<td>1.00</td>
</tr>
<tr>
<td>&quot;Propellant S&quot; (as defined by Example 20)</td>
<td>98.00</td>
</tr>
</tbody>
</table>

Example 37

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenochrome, crystalline, micronized</td>
<td>1.785</td>
</tr>
<tr>
<td>&quot;Span 85&quot;</td>
<td>1.00</td>
</tr>
<tr>
<td>&quot;Propellant S&quot; (as defined by Example 20)</td>
<td>97.215</td>
</tr>
</tbody>
</table>

Example 38

Phenylephrine hydrochloride, crystalline, micronized | 0.253 |
Neomycin sulfate, crystalline, micronized | 0.080 |
Methapyrilene hydrochloride, crystalline, micronized | 0.198 |
Anhydrous sodium sulfate, crystalline, micronized | 0.150 |
"Span 85" | 1.00 |
"Propellant X" (as defined by Example 29) | 98.319 |

The terms and expressions which we have employed are used as terms of description and not of limitation, and we have no intention, in the use of such terms and expressions, of excluding any equivalents of the features shown and described or portions thereof, but recognize that various modifications are possible within the scope of the invention claimed.

1. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form comprising about 0.01% and 20% by weight of a finely-divided powder of a particle size less than about 100 microns suspended in a liquefied propellant having a vapor pressure of at least about 13 lbs. per square inch gauge at 70°F., and between about 0.1 and 20% by weight of a liquid, non-ionic surface-active agent having a hydrophilic-lipophilic balance ratio of less than about 10 and being soluble in said liquefied propellant; said finely-divided powder being substantially insoluble in the mixture of propellant and surface active agent; and when said finely-divided powder is water-soluble, said composition shall contain not more than about 300 parts per million of moisture.

2. A self-propelling, powder dispensing composition as defined by claim 1, wherein the powder has a substantially uniform particle size of less than about 25 microns.

3. A self-propelling, powder dispensing composition as defined by claim 1, wherein the surface active agent has a hydrophilic-lipophilic balance ratio of between 1 and 5.

4. A self-propelling, powder dispensing composition as defined in claim 1, wherein the finely-divided powder shall constitute between about 0.05% and 10% by weight and the liquid, non-ionic surface-active agent between about 0.1% and 5% by weight of the total composition.

5. A self-propelling, powder dispensing composition as defined by claim 4, wherein the surface active agent is an ester of a polyhydroxy compound.

6. A self-propelling, powder dispensing composition as defined by claim 4, wherein the surface active agent is a fatty acid ester of sorbitan.

7. A self-propelling, powder dispensing composition as defined by claim 4, wherein the surface active agent is an unsaturated fatty acid ester of sorbitan.

8. A self-propelling, powder dispensing composition as defined by claim 7 wherein the surface active agent is an oleic acid ester of sorbitan.

9. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises a member selected from the class consisting of prednisolone and its esters.

10. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises a member selected from the class consisting of epinephrine and its salts.

11. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises a salt of isoproterenol.

12. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises isoproterenol sulfate.

13. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises isoproterenol hydrochloride.
14. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises a mixture of phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and methapyriltone hydrochloride.

15. A self-propelling, powder dispensing composition as defined in claim 8 wherein the finely-divided powder comprises a mixture of phenylpropanolamine hydrochloride, phenylephrine hydrochloride, neomycin sulfate and hydrocortisone.

16. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises glucagon.

17. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises cyanocobalamin.

18. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises chlorotetraacycline hydrochloride.

19. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises adrenochrome.

20. A self-propelling, powder dispensing pharmaceutical composition capable of producing a medication in aerosol form suitable for inhalation therapy, comprising a liquefied non-toxic propellant having a density of at least about 13 lbs. per square inch gauge at 70° F., between about 0.01% and 20% by weight of a finely-divided therapeutically active powdered medication of substantially uniform particle size of less than about 100 microns suspended in said propellant, and between about 0.1% and 20% by weight of a liquid non-toxic non-ionic surface active agent having a hydrophilic-lipophilic balance ratio of less than about 10 and being soluble in said liquefied propellant; said finely-divided powder being substantially insoluble in the mixture of propellant and surface active agent, and when said finely-divided powder is water-soluble, said composition shall contain not more than about 300 parts per million of moisture.

21. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form comprising a composition as defined in claim 1, wherein the specific gravity of the finely divided powder is at least as great as that of the liquefied propellant.

22. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form comprising a composition as defined by claim 1 having "μ" units by weight of a useful substance of specific gravity "μ" as a finely-divided powder and "p" units by weight of an auxiliary solid substance of specific gravity "p" in powdered form suspended in a liquid of specific gravity "ρ", wherein the minimum value of "μ," "p," is expressed as follows:

\[ \text{minimum value of } \mu = \frac{\rho_{PA}}{\rho_{PA} - \rho} \]

23. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form according to claim 22, wherein the amount of "μ" lies between the value of "μ min," and 10 times "μ min."

24. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form according to claim 22, wherein the amount of "μ" lies between the value of "μ min," and 3 times "μ min."

25. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form according to claim 24, wherein the useable substance is a medication and the auxiliary solid is a non-toxic powdered substance of particle size less than 25 microns.

26. A self-propelling powder dispensing composition capable of producing a useful substance in aerosol form according to claim 22, wherein the auxiliary solid is sodium sulfate.

27. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form according to claim 22, wherein the auxiliary solid is calcium chloride.

28. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form according to claim 22, wherein the auxiliary solid is lactose.

29. A self-propelling, powder dispensing composition capable of producing a useful substance in aerosol form according to claim 22, wherein the auxiliary solid is sucrose.

30. A package comprising a pressure-tight container with a controlled opening and containing a pharmaceutical composition capable of delivering a measured dose of medication in aerosol form suitable for inhalation therapy, comprising a composition as defined by claim 20.

31. A self-propelling, powder dispensing composition as defined by claim 8 wherein the finely-divided powder comprises adrenocorticotropic.

References Cited in the file of this patent

UNITED STATES PATENTS
2,594,296 Dantrebande Apr. 29, 1952
2,728,495 Eaton Dec. 27, 1955
2,782,975 Bird Feb. 26, 1957
2,959,525 Beard Nov. 8, 1960

OTHER REFERENCES
UNITED STATES PATENT OFFICE
CERTIFICATION OF CORRECTION

Patent No. 3,014,844

December 26, 1961

Charles G. Thiel et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 2, line 46, for "a" read -- the --; line 47, before "mixture" insert -- agent --; column 3, line 68, for "usch" read -- such --; column 4, line 12, for "aand" read -- and --; column 5, line 21, for "vol." read -- Vol. --; column 6, line 56, after "of" insert -- the --; column 7, line 67, for "membrane" read -- membrane --; column 9, line 19, for "dichlorotetrafluoroethane" read -- dichlorodifluoromethane --; column 9, lines 25, 47, 57, and 67, column 10, lines 3, 12, 23, 33, 58, and 67, column 11, line 3, 10, 19, 40, and 68, column 12, lines 3, 10, 18, 27, 36, 47, 56, and 69, column 13, lines 6, 14, 32, 48, 54, 62, and 70, and column 14, line 3, the word "Percent" should be inserted as a heading in the amounts set forth in the right-hand columns, each occurrence; column 12, line 50, for "Lactose" read -- Lactose --; column 14, line 43, column 15, lines 7 and 42, "in," each occurrence, read -- by --; column 16, line 3, for "valve" read -- value --; same column line 57, for "pages 324, 328" read -- pages 324 through 328 --.

Signed and sealed this 24th day of April 1962.

(SEAL)
Attest:

ESTON G. JOHNSON
Attesting Officer

DAVID L. LADD
Commissioner of Patents
UNITED STATES PATENT OFFICE
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