Nov. 3, 1964 F. FOWLER 3,155,573

INHALANT COMPOSITION AND METHOD OF MAKING SAME

Filed Feb. 26, 1959 3 Sheets-Sheet 1

Fig. 1.

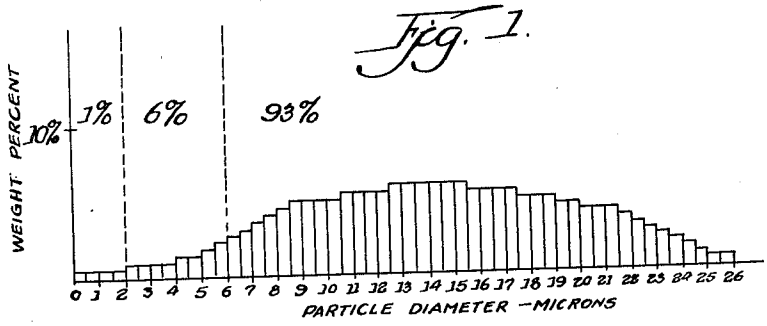


Fig. 2.

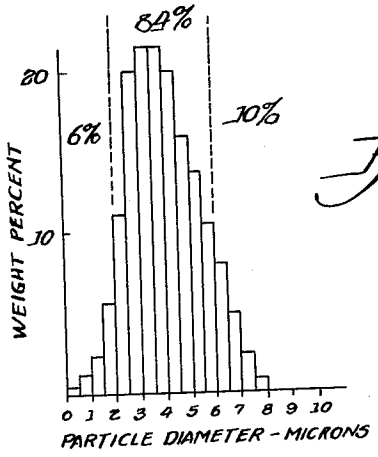


Fig. 3.

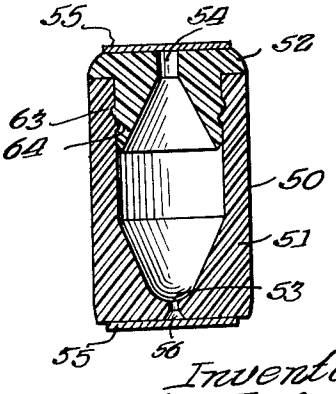
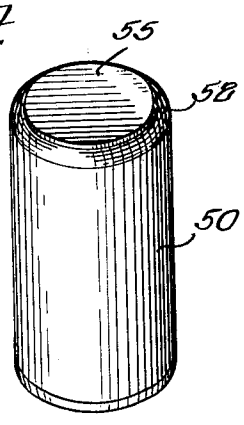


Fig. 4.



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INHALANT COMPOSITION AND METHOD OF MAKING SAME

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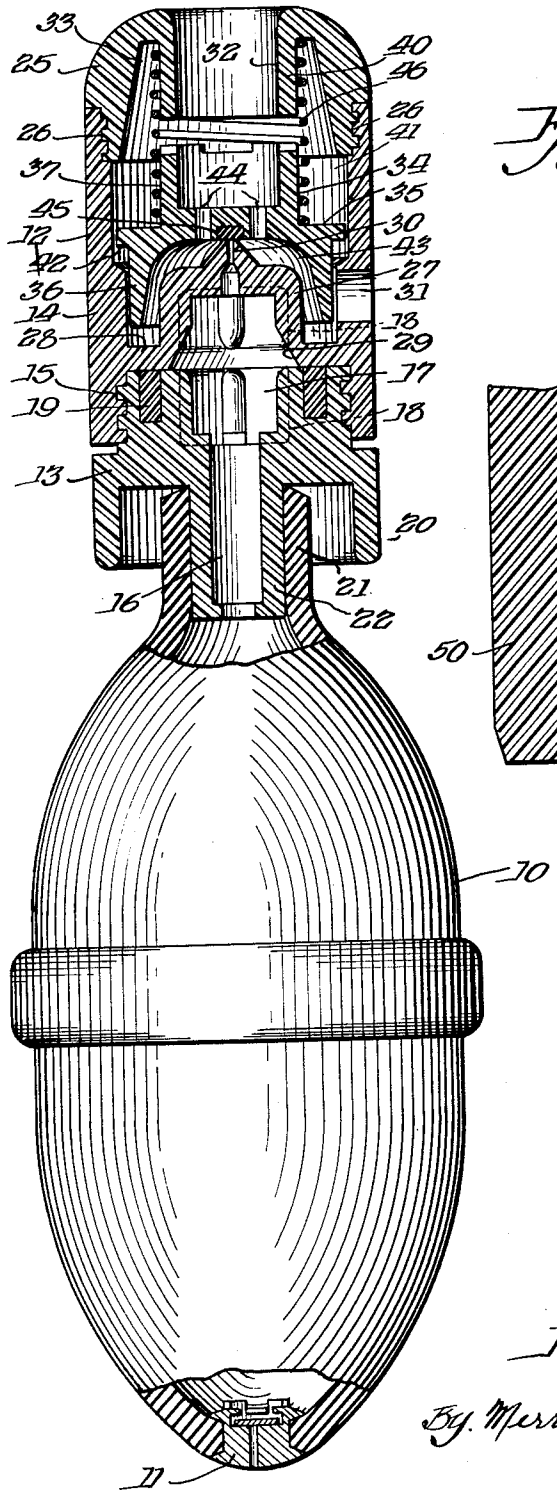

Fig. 6.

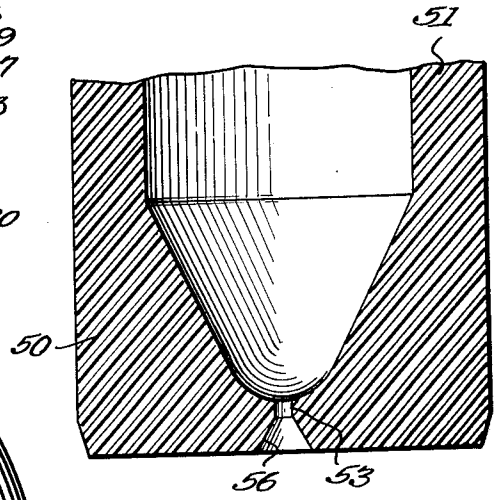

Fig. 5.

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INHALANT COMPOSITION AND METHOD OF MAKING SAME

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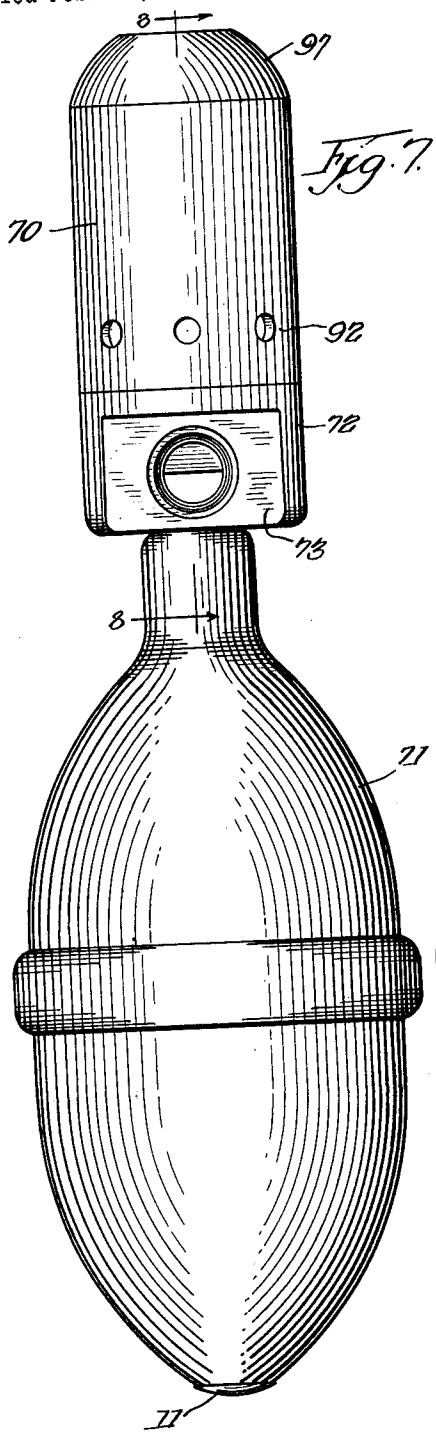

Fig. 7.

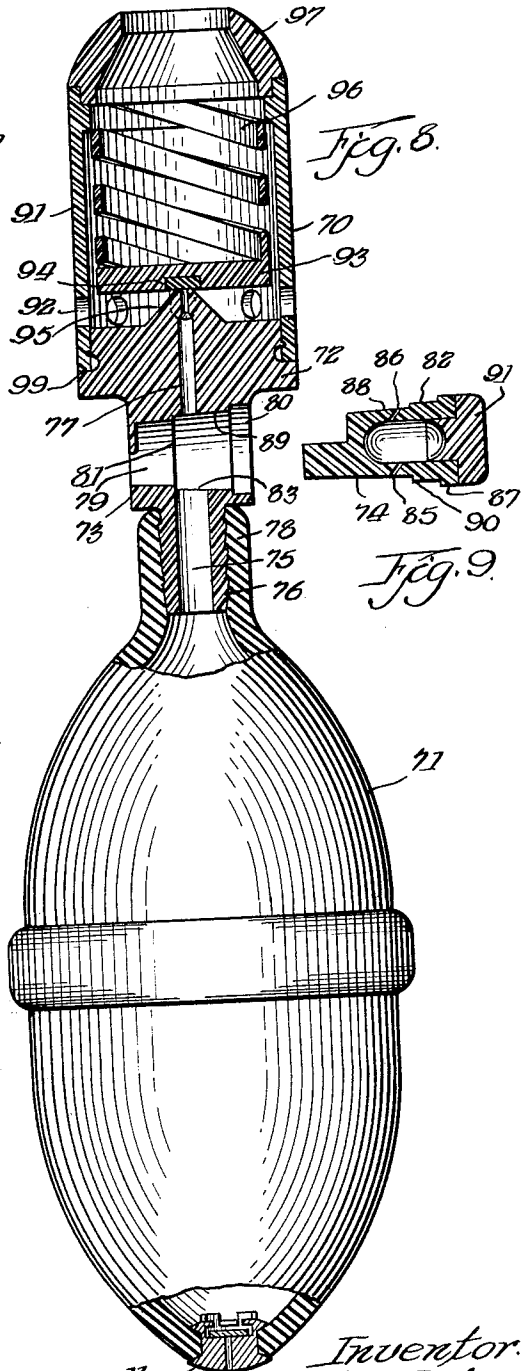

Fig. 8.

Fig. 9.

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United States Patent Office 3,155,573 Patented Nov. 3, 1964

3,155,573

INHALANT COMPOSITION AND METHOD OF MAKING SAME

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Filed Feb. 26, 1959, Ser. No. 795,855
Claims priority, application Great Britain May 6, 1958
3 Claims. (Cl. 167—54)

This invention is concerned with a medicament or drug in the form of a homogeneous ultra fine powder which can be deposited in the deeper parts of the lung following inhalation of air or a gas containing the said ultra fine powder in suspension. The invention is also concerned with novel apparatus and methods of administering such powders.

This special form in which the drug or medicament is supplied results in better utilization of the medicament in that the drug is deposited exactly at the site desired, and where its action may be required, and hence very minute doses of the drug are often equally efficacious to larger doses administered by other means, with a consequent marked reduction in the incidence of undesired side effects. Alternatively, the drug in this special form may be used for the treatment of diseases other than those of the respiratory system. When the drug is deposited on the very large surface areas of the respiratory system it may be very rapidly absorbed into the blood stream, hence this method of application may, in suitable cases, take the place of, for example, administration by injection, tablet, capsule or other means.

Various materials are often manufactured in the form of powders and in many cases the degree of fineness is of great importance in the utilization of such material. These fine powders are most often produced by protracted grinding and sieving operations, the coarser material being recycled through the grinding machine until a sufficiently fine powder is obtained. Casual examination of such fine powders under the microscope may appear to show that the majority of the material is composed of the smaller particles present, but this means of assessment can be quite misleading. Visual examination takes into account mostly the numbers of particles of the different sizes present, whereas what is often required is a knowledge of the proportion by weight of the material which exists at a certain particle size. In the following description, therefore, the description of powder finess refers to the proportion by weight of the material of a certain particle size which occurs in the sample.

One method of determining the particle size distribution by weight consists of thoroughly dispersing a sample of the powder in air and then allowing the powder to settle out completely by gravity on to a microscope slide (for example, if the sample of air containing the dust or powder in suspension has a depth of 2", then about two hours are allowed to elapse to ensure complete settling of the powder). The diameters of several thousand random particles are then measured under the microscope and the diameter cube is taken as a measure of the relative weight of each particle. The individual particle measurements are then sorted into size groups and a "size distribution by weight" diagram constructed. From such graph the proportion of the powder by weight between any two given limits of particles size diameter may be determined. This method is quite reliable except in the case of those powders which contain a considerable proportion of their weight composed of particles with a diameter below 1 micron in size, but as will be seen later, this invention is not concerned with such powders.

For a full understanding of the invention which is described hereinafter in detail, it should be recalled that the human respiratory system commences with a single large diameter tube and after many bifurcations terminates in many thousands of very small diameter tubes (approxmiately 0.6 mm. bore). The large primary tubes also have appreciable length, whereas the terminal sub-divisions are quite short in length. On the other hand, the larger tubes are few in number and have a very small total surface area (of wall) compared to the very large total surface area of the thousands of small tubes. The various types of tubes which occur are described by terms such as: main bronchi, primary bronchi, secondary bronchi, tertiary bronchi, bronchioles, respiratory bronchioles, alveolar ducts and alveolar sacs.

This invention is chiefly concerned with the application of some powders containing drugs to the surfaces of the tubes classed as bronchioles and respiratory bronchioles, which are the smaller and more distal parts of the branched system, with a minimum proportion deposited in the trachea and main bronchi alveolar ducts and sacs, either for the treatment of local disease, or for the purpose of obtaining rapid and complete absorption of the drug into the blood stream.

It has been variously reported and is well accepted that particles of solid, or droplets of liquid, with a diameter exceeding 10 microns cannot be carried by inspired air in any significant degree beyond the secondary or tertiary bronchi. This may be looked upon as a quite reliable natural defense mechanism against invasion of the deeper and effective parts of the lung by foreign matter in the air such as dust, bacteria, etc. It is also fairly well established that particles of dust or smoke with a particle size diameter of less than 1 micron will very readily pass along the tubes to the most distant parts of the lung, namely the alveolar ducts and sacs, but the smaller particles in this range are probably not deposited at all, but return with the exhaled air.

While it has been proposed to make liquid droplet aerosols for respiratory action of a predetermined size, maintenance of droplets in any particular size is impossible and the administration thereof, under the most favorable conditions, cannot be accomplished in home treatment.

At the present time certain drugs are available in a finely powdered form and are intended to be dispersed into the inspired air with the object of treating the nasopharyngeal and buccal membranes and in some cases the trachea, or larger passages. These powders usually have a weight average size of about 10–20 microns and only a small proportion by weight is composed of particles in the range of 2–6 microns, typical powders usually having only 1–10% of their weight within the range of particle diameters 2–6 microns. If one attempts to reduce further the size of such fine powders in order to obtain a larger proportion of their weight within the range of 2–6 microns, as by traditional grinding processes, one finds that much of the material is reduced to a particle size below 2 microns and thus again is rendered ineffective for my purpose, or it may be disadvantageous in other ways. Furthermore, if one attempts to separate the particles having a diameter between 2 and 6 microns from a large number of particles of other diameter by special means such as air flotation, the yields obtained are insignificant or trivial. It is very difficult indeed to reliably obtain or separate only those particles having a diameter between 2 and 6 microns without at the same time obtaining a considerable proportion of other particles, either accidentally or, for example, by occlusion or agglomeration.

This invention provides a homogeneous ultra fine powder in which the particles are mutually non-adherent in which at least a major proportion, and advisably about

two thirds of the powder, by weight is composed of particles having a diameter between 2 and 6 microns. Approximately 80% by weight should preferably be between these limits with the peak of the weight distribution curve approximating the 3 micron size. The powder should contain substantially no particles larger than 10 microns, or preferably no larger than 9 microns, and in any event only a very minute proportion by weight of the particles should be over 10 microns in size, and only a negligible proportion by weight of the particles should be smaller than 1 micron. In any case, the proportion by weight below 2 microns should be less than 20%, or preferably less than 10% by weight, so that the product is substantially free from particles appreciably smaller than 2 microns. The powder should advisably have less than 10% by weight of particles having diameters below about 1 micron.

The advantage of employing a homogeneous powder of this type may be demonstrated quantitatively in several ways. For example, it can readily be shown that when the powder of this invention is inhaled as on a gas or air supported stream, the dosage required to produce a given desired result may be reduced by as much as 75–95% with the fine homogeneous particles as compared with, for example, a powder of the so-called 300 mesh size, i.e., as obtained by grinding and sieving through a 300 mesh per inch sieve administered in the same way.

The following table shows quantitatively the theoretical distribution of an insufflation powder through the various areas of the bronchial system when the particles are of various sizes. It will be noted that with particles of 3 micron diameter the bronchioles and respiratory bronchioles may be expected to receive and retain 46% by weight of the material as compared to only 11% in the case of a 1 micron powder and only 10% for a powder composed of 10 micron particles.

TABLE SHOWING PERCENTAGE BY WEIGHT OF A POWDER OF SPECIFIED PARTICLE SIZE WHICH WOULD BE EXPECTED TO BE DEPOSITED IN THE DIFFERENT REGIONS OF THE LUNG

	Size of Powder			
	30 microns	10 microns	3 microns	1 micron
Trachea and main bronchi	90	46	6	1
Primary and secondary bronchi	10	35	8	1
Tertiary bronchi	0	9	5	2
Bronchioles	0	10	27	5
Respiratory bronchioles	0	0	19	6
Alveolar ducts	0	0	35	42
Alveolar sacs	0	0	0	41
Exhaled	0	0	0	3

When compared with existing fine powders (usually these prior art powders are only intended for the treatment of the naso-pharyngeal and buccal membranes) a very marked advantage is found. For example, when isoprenaline sulphate is used in the form of a powder which been prepared by a grinding process and so has a very disperse particle size and where the powder would be classed as "passing a 300 mesh sieve," it is found necessary to give a dose of about 2 mgm. in order to obtain a maximum effect when measured as the degree of bronchodilation attained in an asthmatic patient. The same patient will obtain maximum bronchodilation when given a dose of only 0.05 mgm. of isoprenaline sulphate in the form of the fine homogeneous powder of this invention. One of the most obvious advantages resulting from the use of the latter is the absence of side effects due to the very efficient utilization of a minimum sized dose.

The composition and concentration of the powders of 2 to 6 microns provided by this invention can be selected and altered according to the particular type of disease to be treated. Essentially any medicament can be administered as an insufflation powder of the required particle size of 2 to 6 microns as defined previously. The powder may be composed entirely of the medicament or the medicament may be diluted as by combining its with a suitable pharmaceutically acceptable carrier to give a more convenient volume-to-active agent relationship. A combination of medicament and carrier may be a physical mixture of both substances of the required particle size or the carrier may be coated on the surface with, or be impregnated by, the medicament. One of the most suitable carriers that may be used is dextran.

A typical insufflation powder of the required particle size may be composed of 5 mgm. of chymotrypsin and 10 mgm. of a low molecular weight dextran fraction on which is absorbed 1% of isoprenaline sulphate (0.1 mgm.). Such a composition is useful for treatment of chronic bronchitis, particularly those cases with an excess of thick viscous secretion. A similar powder but without the chymotrypsin can be used as an insufflation powder for the rapid relief of bronchospasm.

There is also provided by this invention a novel way of preparing such homogeneous ultra fine powders and this novel method is considered capable of producing almost completely homogeneous powders with, for example, 90% by weight of the particles having a diameter of 3 to 4 microns. The process, however, readily provides homogeneous powders of which four-fifths of the weight is composed of particles from 2 to 6 microns while the remaining one-fifth by weight lies quite close to these limits and so is also somewhat effective.

This novel process consists essentially of two steps, firstly, the drug is precipitated from solution so that the particle size is mostly from 2 to 6 microns, or alternatively, the drug is absorbed on an inert water soluble carrier which itself has a particle size from 2 to 6 microns (a suitable carrier is, for example, a low molecular weight dextran, i.e., a 1:6 polyglucose). The second stage of the process consists of converting this wet precipitate into a dry powder without the formation of aggergates other than perhaps a loose physical agglomeration which is easily dispersed in the apparatus described subsequently herein.

It has been found that when a solution of a water soluble drug is precipitated by a water miscible solvent in which the drug is insoluble, there is a minute fraction of time before which the now theoretically insoluble drug is precipitated in particulate form. At this moment of time the drug is dissolved in the mixed solvents in an extremely super-saturated form and the particle size in which it will appear when it precipitates can be controlled partly by the degree of homogeneity obtained in the super-saturated state and partly by other treatment of this super-saturated solution such as by ultrasonic vibration or the recycling of a proportion of the already formed precipitate as a source of nuclei for the seeding of the further precipitate.

The finely sub-divided drug obtained by precipitation or absorption on a preformed precipitate of suitable inert material may then be transferred by procedures such as filtration or decantation into other solvents with different physical characteristics. For example, if the drug is originally in aqueous solution it may be precipitated in the first place by ethyl alcohol and the suspension in the water-alcohol mixture may then be washed or decanted to obtain a suspension in dry ethyl alcohol by the addition of further alcohol in portions, etc., and in turn this dried ethyl alcohol could be changed to dry butanol or to a petroleum fraction such as petroleum ether, boiling point 120° C., or in fact, almost any other solvent in which the drug or inert carrier, if present, is insoluble. The invention consists, insofar as the drying stage is concerned, of two parts, firstly, the utilization of a solvent (from which the powder will ultimately be dried) in which the drug or inert carrier has minimal solubility, so that there is the smallest possible amount of material remaining in the

last portion of the solvent to be evaporated and hence minimal effect in producing a cement-like material between adjacent particles. Secondly, in most cases it is advantageous to choose a solvent which may be fairly readily frozen and removed by vacuum distillation or vacuum sublimation. Thus, the material which is transferred to the final stage of drying would, in a typical case, consist of a paste containing perhaps one quarter of its weight composed of the finely sub-divided drug precipitate and the remaining three quarters of its weight being, for example, tertiary butyl alcohol, being a solvent in which the drug has minimal solubility. The cementing effect of the material still remaining in solution in this butyl alcohol can then be minimized by extremely rapid freezing of the precipitate tertiary butyl alcohol paste so that the crystal size of the tertiary butanol is as small as possible. This ensures that the small amount of material in solution, which will be present in the last portion of solvent to freeze and so be at the interface of the solvent crystals, will be spread over as large a surface area as possible and hence will be in the most delicate physical form when the solvent has been removed. These small residual amounts of solute, therefore, cease to have any appreciable "cementing" properties between the particles of precipitate. The resulting dried product consists of a very fine, loose, evenly textured powder, immediately suitable for dispersal into the inspired air without any grinding, sieving or other traditional processes.

A specific application of this method is shown by the following examples:

Example 1

Fifteen grams of a dextran fraction of a molecular weight of approximately 10,000 are dissolved, together with 1.25 g. of isoprenaline sulphate in 100 ml. of water. This solution is run at a rate of 3 ml./minute simultaneously with 94% w./w. ethyl alcohol at a rate of 48 ml./minute into a suitable vessel of capacity 500 ml. fitted with a top run-off and an efficient stirrer such as a homogenizer. The resulting suspension is filtered, resuspended in 100 ml. of 99% w./w. tertiary butyl alcohol, filtered once more and again resuspended in 100 ml. of 99% w./w. tertiary butyl alcohol. The tertiary butyl alcohol suspension is rapidly frozen and the resulting solid freeze dried. A free flowing ultra fine powder is obtained, in which approximately 80% by weight is composed of particles between 2 and 6 microns diameter.

Example 2

Five grams of chymotrypsin (assaying at 14 Anson units per gm. protein nitrogen) is dissolved in 100 ml. of distilled water. By a similar technique to that given in Example 1, this solution is mixed with 250 ml. of absolute tertiary butyl alcohol. The resulting suspension is filtered, resuspended in 100 ml. of 99% w./w. tertiary butyl alcohol, filtered once more and again resuspended in 100 ml. of 99% w./w. tertiary butyl alcohol. The butyl alcohol suspension is rapidly frozen and the resulting solid freeze dried. A free flowing ultra fine powder is obtained, in which approximately 80% by weight is composed of particles between 2 and 6 microns diameter.

In the accompanying drawings FIGURE 1 shows the particle size distribution by weight of a typical known powder classed as "passing a 300 mesh sieve," while FIGURE 2 shows the corresponding distribution of a preferred powder in accordance with the invention.

Although the novel fine powders of mutually non-adherent particles of 2 to 6 microns provided by this invention can be administered by the use of known procedures and with existing devices, it is considered that all of the prior art methods and apparatuses have serious deficiencies. For proper administration of these powders they should be thoroughly dispersed so that each particle is separately suspended in the inspired air or gas (oxygen) in order to obtain the desired effect. Not only must the powders be properly suspended, but they must be administered only during inhalation, and not during exhalation or when a person is momentarily holding his breath, for the particles to be drawn in sufficiently to reach the desired respiratory areas.

There is, accordingly, also provided a novel disperser for administering these powders, as well as a novel cartridge containing the powders which can be used in conjunction with the disperser. These devices will now be described in conjunction with the attached drawings in which:

FIG. 3 is a cross-sectional view in elevation of a cartridge;

FIG. 4 is a perspective view of the cartridge shown in section in FIG. 3;

FIG. 5 is an enlarged view of the lower portion of the cartridge shown in FIG. 3;

FIG. 6 is an elevational view partly in section of one embodiment of the disperser;

FIG. 7 is an elevational view of another embodiment of the disperser;

FIG. 8 is a view of the disperser of FIG. 7 taken partly in section at the line 8—8 thereof; and

FIG. 9 is a view of a cartridge for use in conjunction with the disperser of FIGS. 7 and 8.

Referring first to the disperser of FIG. 6, which is the preferred device, it will be seen that it comprises a squeeze bulb 10 with valve 11 which lets in air but prevents its escape, and that the bulb is attached to cylindrical mouthpiece 12. The mouthpiece 12 is composed of three main portions which are threaded together into a unitary structure which can be disassembled readily. Forming part of the mouthpiece 12 is the base 13 to which the bulb 10 is attached. Body 14 is threadably engaged 15 to the base 13, and at the other end is threadably engaged to the nozzle portion 25.

The base section 13 contains axial hole 16 and cartridge receiving recess 17 into which approximately the lower half of a powder-containing cartridge fits. The dotted lines 18 signify that grooves are provided in the bottom and sides of the recess 17 so that air may pass around the cartridge as well as go through it. To provide a tight seal between the base section 13 and the body 14, flexible washer 19, as of rubber, is placed in the top of the body portion as shown. Shroud 20 is added to protect the bulb throat 21 and bar it being removed inadvertently from the nipple 22 containing hole 16; the shroud also gives the device a more elegant appearance.

Body portion 14 is generally shaped like a cylindrical shell with internal thread means 15 at the lower end and internal thread means 26 at the upper end. Body 14, however, contains an inverted cup 27 integrally formed therewith by shoulder 28. The cup 27 is flared 29 at its mouth to facilitate entry of the upper part of a cartridge into the cup. It will be readily seen that cup 27 and recess 17 are coaxially positioned and of a size so that together they comprise a cartridge receiving receptacle. The cup 27 contains grooves 18 in the walls and bottom thereof which act as passages for air to pass around the cartridge. The cup 27 has orifice 30 axially located therein and so located as to be in line with and adjacent the egress hole of the cartridge so that the air or gas transported fine particles can be expelled therethrough. The body 14 has side ports 31 which permit air to enter therein.

Nozzle 25 is threadably attached 26 to the body 14 and contains an internal downwardly projecting cylindrical sleeve 40 having throat 32 spaced apart 33 from the outer wall of the nozzle.

Located in the body 14 is a piston 34 comprised of a disc 35, from which cylindrical skirt 36 depends, and also from which cylindrical sleeve 37 projects upwardly in line with sleeve 40. The top of sleeve 37 is castellated so that when it abuts the bottom of sleeve 40 it

will not prevent the application of suction in areas 33 and 41. The disc 35 has a flange 42 which extends outwardly beyond the skirt 36 so that when suction is applied through throat 32 and in area 41, air will enter ports 31 and apply pressure against the flange 42 and thus force the piston upwardly. As the piston moves upwardly the bottom edge of skirt 36 is raised permitting air to flow therebeneath and into area 43 where it combines with the air-transported particles coming out orifice 30 and facilitates dispersing the particles and transporting them through holes 44 in the disc portion 35 of the piston and through throat 32 into the respiratory system of an inhaling person. Pad 45 is located in the bottom of the disc 35 to provide a good seal of orifice 30 when the piston is at rest. Spring means 46 extends around sleeves 37 and 40 and urges the piston away from the nozzle portion. The tension of the spring is carefully selected so that it will maintain the piston down until a person creates a suction, as by inhaling with the mouthpiece in his mouth, in the area 41 after which atmospheric pressure forces the piston upwardly by air entering ports 31.

The disperser is advisably made of nylon except for the bulb, washer and pad which can be rubber, while the spring may be steel.

Shown in FIGS. 3, 4, and 5 are views of a cartridge 50 which can be used in the disperser of FIG. 6 and which fits in the receptacle formed of recess 17 and cup 27. The cartridge has a cylindrical body portion 51 having a tightly fitted cap 52. The cartridge has an internal cylindrical cavity tapered at both ends into conical areas with the end portions of the cones adjacent the top and bottom ends of the cartridge. The tapered areas assist in the ejection of all of the contents in the cartridge and thereby assure utilization of the entire dosage. The bottom of the body portion is provided with a small opening 53, preferably about $\frac{1}{64}$ of an inch in diameter. Cavity 56 is provided as part of the ingress hole to facilitate molding. This opening 53 (the ingress opening) is for the injection of air into the cartridge. The cap 52 is provided with opening 54, preferably about $\frac{1}{32}$ of an inch in diameter for ejection of the powder from the cartridge by means of the air injected at the bottom. Adhesive sealing discs 55, as of polyethylene, are applied to the ends of the cartridge to bar access of moisture to the powder in the cartridge. These discs are removed before the cartridge is placed in the disperser.

A typical cylindrical cartridge may be about 13 mm. long and about 8 mm. in diameter with an air ingress hole of 0.20 to 0.25 mm. and a combination particle and air egress hole of 0.8 to 1.0 mm. The ends of the cylinder in which the holes are located are conically shaped internally with the cone tops directed to the cartridge ends. The air ingress hole can have a wall length of about 0.25 mm. and the egress hole a wall length of about 1 mm.

The powder is packed lightly in these cartridges in such a manner as to be free-flowing in the air which is used to remove it, and yet is loosely aggregated so that the holes at either end of the cartridge are small enough to ensure that the powder does not flow out under ordinary handling conditions. Such cartridges are preferably moulded from a plastic material, such as polyethylene, which amongst other properties has that of preventing the passage of moisture vapor to a remarkable degree and as these very fine powders may be damaged in the case of certain drugs by moisture, this can be a marked advantage.

This apparatus serves at least two functions, it disperses the powder completely into the inspired air and, secondly, it only releases the powder when the patient is making a sufficiently strong inspiratory effort. The rubber bulb delivers approximately 50 cc. of air at a pressure of 6–8 lbs. per sq. in. About one tenth of this air passes through the cartridge and transfers some of the powder into a small mixing chamber where the remaining nine tenths of the air are used in the form of impinging jets to cause a very intense local turbulence which breaks up the loose power aggregates into separate particles. From this chamber there emerges, therefore, a 50 cc. quantity of a very concentrated powder smoke.

When the patient commences to breathe in through the mouthpiece he finds that only a very small quantity of air can be obtained and hence he can very quickly build up a strong suction in the apparatus. When the degree of suction reaches a certain value the valve is "triggered" and air flows into his lungs at a rate of 2 or more liters per second. The patient is able to maintain this rate of flow from between 0.5 and 1.0 second during which time he has inspired between 1 to 2.5 liters of air. It is during the first 0.3 second that the 50 cc. of concentrated powder smoke is injected into the air flowing during that period of time—i.e., into approximately 0.8 liter of air. It will be seen, therefore, that even in the case of a severely disabled patient having a small inspiration there will still be an appreciable amount of further air inspired after the end of the powder addition. This further air helps to ensure that the 0.8 liter of air containing the powder is transferred into the deeper parts of the lung.

This device was found to be very satisfactory in practice. The effect produced is to cause the patient to make a strong inspiratory effort without at the same time filling his lungs prematurely with air and only when he is making a sufficiently strong effort can he get both the air and the dose of powder.

The disperser of FIG. 6 is preferred to that of FIGS. 7 and 8 since the former requires less air intake to open the valve and is easier to clean since the spring 46 is protected and out of the path of the air-transported particles. Furthermore, by having the atmosphere apply pressure initially only against the flange 42 instead of the entire area of the disc, it requires more suction to open the valve compared to the suction necessary to maintain it open than in the device of FIGS. 7 and 8 which, as a result, causes the powder to be inhaled more deeply.

The disperser as shown in FIG. 6 is about 2 times scale so that it will be readily appreciated that the device is suitable for carrying by a person in a coat pocket in order that the insufflation powder can be self-administered at any location convenient to the patient, such as at home or his place of business.

A second embodiment of a disperser is shown in FIGS. 7 and 8 and a capsule for use in conjunction with the disperser is shown in FIG. 9.

The disperser of FIGS. 7 and 8 has a mouthpiece 70 connected to bulb 71. The mouthpiece 70 has a cylindrical end section 72 through which an axial duct 77 passes to the discharge orifice. An intermediate section of said end section 72 is formed with two opposed parallel faces 73, the disposition of which is chordal with respect to the cylindrical projection of the end section 72. Between the faces 73 a socket recess 79 for receiving cartridge 74 extends transversely so that the duct 77 ($\frac{1}{16}$" at lower part and $\frac{1}{32}$" at top) opens into it. Beyond the socket recess a nozzle 76 having hole 75 ($\frac{1}{8}$") is engaged with the mouth 78 of the bulb. The bore of hole 75 is on the same axial alignment as duct 77 so as to open into the recess 79.

The socket recess 79 is generally cylindrical with one end fully open and sunk into one of said faces 73 with the other end partially narrowed or closed so as to leave a slot in the other face. The socket recess 79 is stepped down in diameter 81 on the far side of the duct 77 and hole 75.

The cartridge 74 for mounting in the recess is formed externally as the socket recess except that the area 88 of the cartridge is smaller than the near side 89 (biggest diameter in the socket) of said duct 77 and hole 75 to thereby create an annular passage 83, of general ring shape, between the two steps 81 and 90 and around the cartridge. The orifices 85 and 86 in the cartridge are positioned to register with the hole 75 and duct 77 respec-

tively and to be located in the annular passage **83**. By making the depth of the steps and the distance between them such that the resulting cross-sectional area is about four and one-half times as large as orifice **85** (1/64") or **86** (1/32") whichever is bigger, roughly nine times as much air will be diverted around the capsule as can pass through it in a certain period.

In order to ensure a tight fit of the cartridge within the socket recess, the mating surfaces of both, outside the passage zone between the steps, may be tapered slightly towards their far or inner ends. The near or outer end of the cartridge is flanged **87** for engagement within the sunk face opening **80** of the recess. The filling mouth of the cartridge is provided with a suitable stopper plug **91** externally formed with a button by which the capsule can be readily pressed home into the recess. The far or inner end of the cartridge is formed with a projecting key adapted to fit and project through the slot in the far end of the recess to properly align the orifices with hole **75** and duct **77**.

The cartridges can be supplied for use in the disperser, each removably mounted, in individual tubular sheaths which may also be of plastic and, can, if desired, be combined to any required number into a plate with the sheaths projecting as sockets from its face. The orifices of each cartridge are thus kept sealed, by the wall of such sheath or socket, and the contents protected from deterioration and, what is particularly important with very fine powders, from dampness such as might cause caking.

The mouthpiece is provided with a tubular sleeve **91** axially projecting around the discharge duct, the inner end of which sleeve may be detachably secured to a shouldered seating **99** on said end section. Immediately adjacent the end of the latter, the sleeve has air intake openings **92**. Loosely fitting within the sleeve is a disc **93** serving both as a piston baffle and as a valve member, for which last mentioned purpose said disc is provided with a central sealing pad **94** which normally seats against and closes the discharge duct **77**. By disposing this duct at the tip of an axial conical projection **95** of the body, said disc is maintained clear of said zone of sleeve openings on the upper or suction side of the intake openings. The disc is urged downwardly into seating engagement with the duct by a coil compression spring **96** of about the same diameter as the disc itself, which spring may be anchored just within the open end of the sleeve **91** and said spring and disc can, if desired, be formed integrally with the sleeve as a single moulding. The strength of the spring is such that it allows the disc to be lifted from the discharge duct by an air current drawn, by appropriate suction at the nozzle **97** end of the sleeve as by placing the mouthpiece in the mouth and inhaling in through the zone of openings and around the edge of the disc, but on the other hand prevents the latter from being raised without, or unassisted by, such suction, merely by pressure obtainable by means of the collapsible bulb acting over the small cross-sectional area of the orifice. The sleeve is suitably finished off as a mouth-piece by fitting its open end with a supplementary domed annulus or nozzle **97**.

Valve **11** is the same as in FIG. 6.

The valve means of the disperser of FIGS. 7 and 8 prevents emission of air-supported powder through duct **77**, even though the bulb **71** is squeezed, until a sufficient air current is simultaneously drawn in through the mouthpiece, thus ensuring against waste of powder as would take place if exhalation, or no inhalation, was taking place. The valve means does this by being differentially operated in the sense that it presents an area to the lifting influence of the inhaled air current which is large in comparison with the very small area it presents for lifting by the air pressure at said orifice. The dics functions as a loosely fitted piston within the mouthpiece and is adapted normally to bear against the orifice through the sealing pad under the influence of gravity and/or the spring, with a force which the opposed air pressure is unable to overcome by itself. Conscious synchronism between inhalation and discharge of the powder-bearing air is thus not required. The valve cannot be opened under the sole influence of pressure in the bulb but can be opened by a predetermined degree of suction caused by the drawing in of air through the mouthpiece.

Various changes and modifications of the invention can be made and, to the extent that such variations incorporate the spirit of this invention, they are intended to be included within the scope of the appended claims.

What is claimed is:

1. A medicament comprising therapeutically active mutually non-adherent solid particles embodying a solid lower molecular weight dextran base carrying a therapeutically active agent selected from the group consisting of isoprenaline and chymotrypsin, the medicament having at least about 80% by weight of the particles with diameters from about 2 to about 6 microns and with less than 10% by weight of the particles having diameters below about 1 micron.

2. A medicament comprising therapeutically active mutually non-adherent solid particles embodying a solid low molecular weight dextran base carrying a therapeutically active agent selected from the group consisting of isoprenaline and chymotrypsin, with a major proportion by weight of the particles having a diameter within the range from about 2 to about 6 microns.

3. The method of producing a medicament as a homogeneous powder of mutually non-adherent particles which comprises dissolving lower molecular weight dextran and a water soluble drug selected from the group consisting of isoprenaline and chymotrypsin in water, combining the aqueous solution with a water miscible solvent in which the dextran and drug are insoluble in sufficient quantity to precipitate the dextran, as solid particles carrying the drug with a major proportion by weight of the particles having a diameter within the range from about 2 to about 6 microns, suspending the precipitated particles in a liquid in which it has minimal solubility by thorough mixing, quickly freezing the suspension and removing the liquid by evaporation under reduced pressure.

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