

[54] **TRIAMCINOLONE ACETONIDE
INHALATION THERAPY**

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[51] Int. Cl.² **A61M 15/02**

[58] Field of Search **128/266, 187, 185, 208, 128/209; 222/420.20, 402.17, 192; 259/DIG. 41; 424/46; 239/338**

References Cited

UNITED STATES PATENTS

3,219,533	11/1965	Mullins	222/192
3,236,458	2/1966	Ramis	239/338
3,285,579	11/1966	Guerin	259/DIG. 44

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979-988, Decadron, Sept. 15, 1972.

Physician's Desk Reference, 1973, 27 Edition, p. 807-814, Aristocort, July 1972.

Lancet, Sept. 5, 1959, The Dosage of Dexamethasone and Triamcinolone in Bronchial Asthma, p. 257-258.

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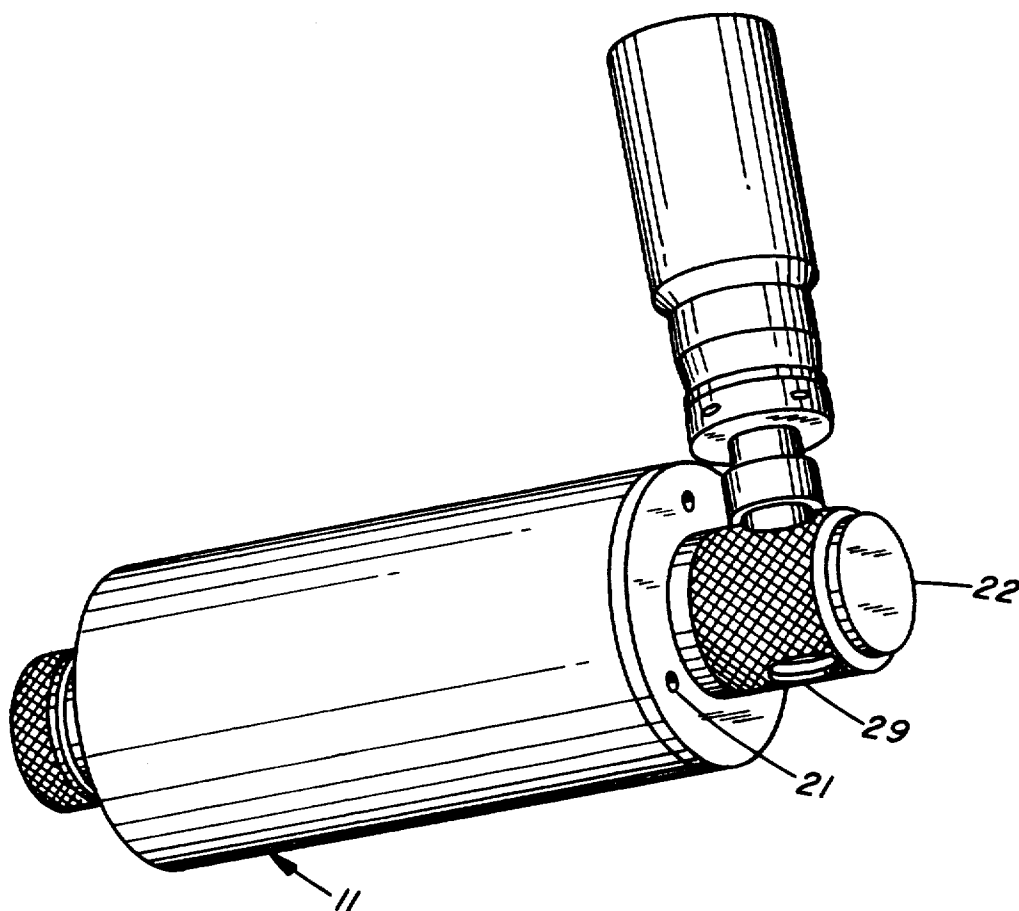
Attorney, Agent, or Firm—Samuel Branch Walker

[57]

ABSTRACT

An aerosol container carrier and deceleration chamber for dispensing powdered triamcinolone acetonide with inhaled particles predominantly below 10 microns in size at a low velocity gives a comparatively high degree of topical effect in the lungs as compared with systemic effect from triamcinolone acetonide absorbed in the mouth or upper throat. The suspension of triamcinolone acetonide in dichlorodifluoromethane is preferably subjected to sonic waves at about -40°C , resulting in a suspension having increased physical stability. A suspending agent such as anhydrous ethanol or sorbitan trioleate also increases stability.

1 Claim, 5 Drawing Figures



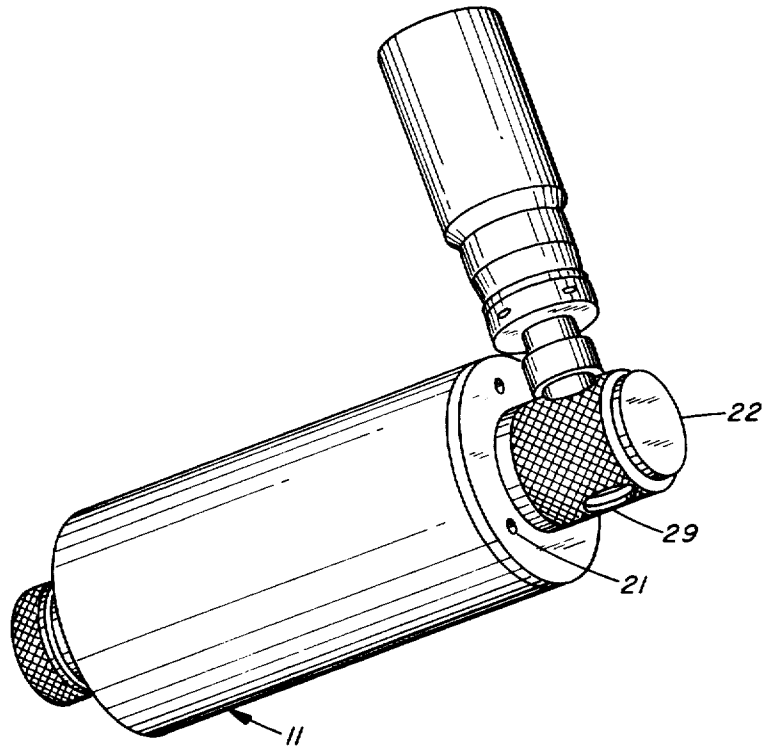


FIG. 1

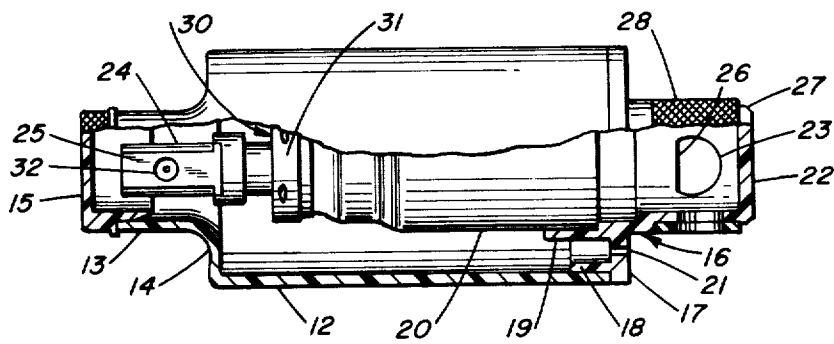


FIG. 2

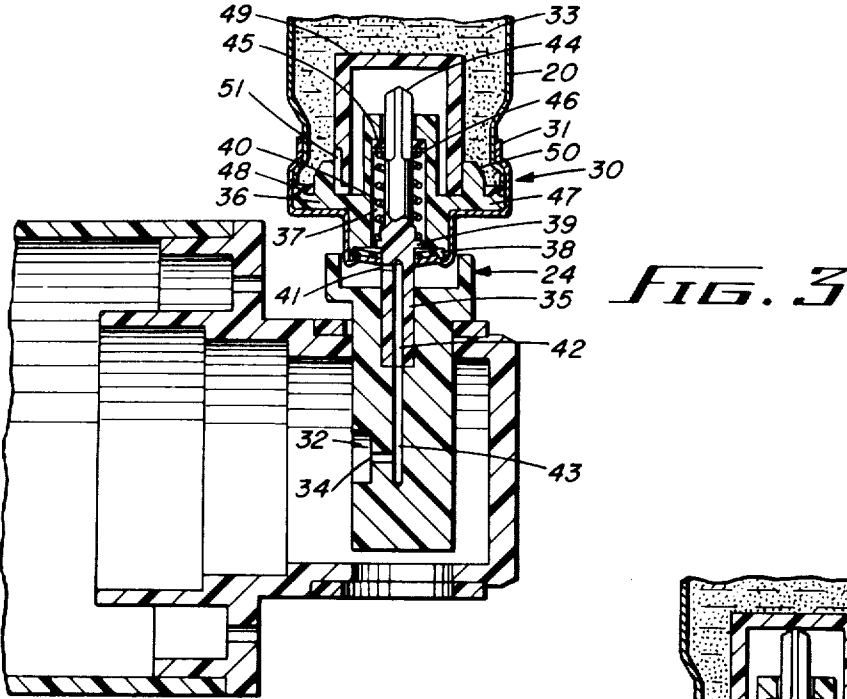


FIG. 3

FIG. 4

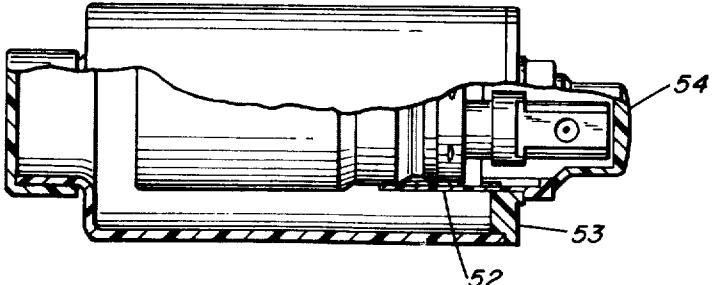
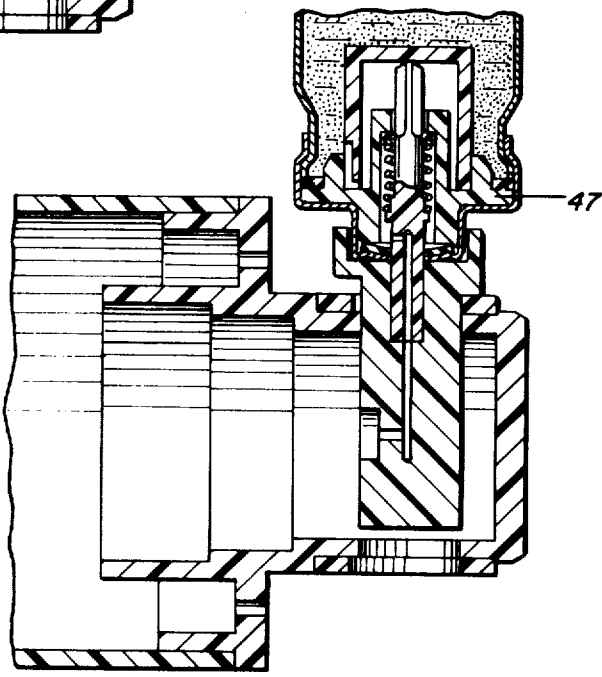


FIG. 5

TRIAMCINOLONE ACETONIDE INHALATION THERAPY

BACKGROUND OF THE INVENTION

The inhalation of medicaments has long been known. There is a continuing effort to secure uniform comparatively accurately measured dosages in selected areas. Large particles have a tendency to be deposited in the mouth or upper throat. Small particles, below about 10 microns, have a tendency to go deeper into the lungs. The problem is to secure the desired dose in the desired area of a desired medicament at the desired time. Sometimes the systemic effect of a drug on other organs is of dubious effectiveness or actually undesired. Steroids such as triamcinolone acetonide have a systemic effect if administered orally and a local effect on the lungs themselves, so it is desirable to be able to administer the triamcinolone acetonide to the surfaces of the lungs only.

SUMMARY OF THE INVENTION

The present invention is based upon the discovery that the discharge from an aerosol container having therein a suspension of triamcinolone acetonide in a propellant can be suspended in dry vaporized propellant mixed with air by the use of a deceleration chamber which is big enough to serve as a carrier for the aerosol container in a storage and transportation configuration and which has a neckeddown mouth-piece at one end and a neckeddown spray system at the other.

Preferably, the triamcinolone acetonide is finely divided, to about 0.5 to 10 microns, and is suspended in dichlorodifluoromethane to give a comparatively high pressure system with improved spray characteristics. If anhydrous ethanol or sorbitan trioleate is used with an ultrasonic energy input, the dispersion of the triamcinolone acetonide in the propellant is improved so as to give a larger proportion of fine particles and fewer larger aggregates; and reduce static effects.

The deceleration chamber is about the same volume as the human oral cavity, with the mouth open. It serves to decelerate the aerosol charge to give a low velocity to the triamcinolone acetonide powder, absorb the aerosol jet momentum before the triamcinolone acetonide powder enters the user's mouth, complete the vaporization of the aerosol propellant, eliminating the possibility of liquid propellant reaching the mouth, dilute the propellant and suspended triamcinolone acetonide powder with air, and give uniform and acceptable powder losses, so that uniform triamcinolone acetonide doses are administered. It is desirable that a major portion of a discharged medicament be administered to the user, but it is more important that each dose be of consistent and predictable size and absorbability so that a known uniform dose is administered with each depression of the actuation button. A considerable percentage of loss is acceptable if reliably uniform. With the present system, losses of about 25 to 50% of the total triamcinolone acetonide dose occur. The deceleration chamber traps much of the triamcinolone acetonide that would deposit in the mouth of the user, so that a relatively small amount of the triamcinolone acetonide is deposited in the mouth as compared to the amount that reaches the lungs, and is effective locally in the lungs.

Additionally, a trap system is used to submerge the metering valve to insure that the metering valve is im-

mersed in the propellant at all times so that the metering chamber does not drain and, in effect, lose its prime. This at times is referred to as a drain-free trap.

The system is particularly effective for use with triamcinolone acetonide which is of value in the treatment of asthma, and which is desirably administered in small known uniform accurate dosages which are absorbed primarily in the lung system as contrasted with the nose and throat. The physiological effectiveness is augmented by increasing the concentration of triamcinolone acetonide administered to the lungs, as compared to that obtained when administered systemically.

DESCRIPTION OF THE PRIOR ART

Certain representative patents in this very crowded field include:

U.S. Pat. No. 2,992,645, Fowler, July 18, 1961, "Dispenser For Powders," in Column 2 has a table showing the effect of particle size on the zone of deposition of a powder in the respiratory tract. Powder sizes of 1 and 3 microns are shown to go deeply into the lungs.

U.S. Pat. No. 3,012,555, Meshberg, Dec. 12, 1961, "Dispensing Package For Material Under Pressure" shows an aerosol liquid dispenser with an operating spray button assembled to the valve stem, which button, with spray orifice, fits removably into an applicator nozzle. In one configuration the applicator nozzle is used for spray control; in another for protective storage.

U.S. Pat. No. 3,219,533, Mullins, Nov. 23, 1965, "Aerosol Solid Medicament In Propellant And Low-Level Ethanol Avoiding Higher-Level Ethanol Dispersed-Solid Reflocculation" shows many solid medicaments, including such steroids as hydrocortisone, prednisolone and dexamethasone dispersed in the particle size range of 0.5 to 10 microns in certain chlorofluoroalkanes using 0.5 to 5.0 % ethanol, for inhalation and ophthalmic therapy.

U.S. Pat. No. 3,236,458, Ramis, Feb. 22, 1966, "Aerosol Apparatus," shows an aerosol liquid dispenser using coaxial concentric extendable tubes for particle size control. The tubes in collapsed position function as a container carrier for storage. In extended position, the mass of air in the tubes impedes the forward flow of a spray and serves as a partial barrier to the discharge jet. The inside diameter is preferably 18 to 30 mm. and the length 3 to 10 times the diameter, preferably 5 to 7 times.

The aerosol container and valve are taken out of the stored position, and the valve stem is inserted into a dispensing spray head which forms the end of the inner tube at the time of use.

Ramis teaches that for inhalation therapy, the particles of the therapeutic agent should be between 0.5 and 5 microns in size, since particles above 5 microns may not reach the air-cells in the lungs while particles below 0.5 microns may fail to be deposited in the lungs. Ramis teaches using dichloro-difluoro-methane as the propellant in which the active product is dissolved or kept in a homogeneous emulsion suspension. The disclosures are limited to soluble products.

Triamcinolone acetonide, 9 α -Fluoro-11 β ,16 α -17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone is described and the formula given in The Merck Index, Eighth Edition, Merck & Co., Rahway, N.J. (1968), pages 1064 and 1065.

In this invention a dispersing package for therapeutic agents under pressure such as shown in Meshberg, U.S. Pat. No. 3,012,555, supra, is modified by adapting a valve to dispense powdered triamcinolone acetonide suspended in the propellant and discharging the nozzle into the entrance of a deceleration chamber having a cylindrical barrel portion, a mouth-piece at the exit end, and container holder-actuating button holder to hold the spray nozzle system.

Preferably, the deceleration and expansion chamber is adapted to completely enclose and hold the aerosol container during storage with the system being assembled in one configuration for storage and transportation and another for use. By having dust covers and sealing means, the assembly in storage and transportation position is protected from contaminating dust and may be conveniently carried in the pocket of a user and yet be rapidly assembled with minimum risk of contamination of the contents at the time of use.

Other advantages will be appreciated by those skilled in the art from the detailed description of a device which permits dispensing of triamcinolone acetonide for lung administration.

DRAWINGS

FIG. 1 is a pictorial view of the aerosol dispenser assembled in dose administering configuration.

FIG. 2 is a view in partial section showing the dispenser in the storage and transportation configuration.

FIG. 3 is an enlarged view in section showing the valve assembled to the expansion chamber cover and particularly, an anti-drain tank to insure that the metering valve is continuously immersed in the propellant and, thus, protected from partial draining and resulting irregular dosages.

FIG. 4 shows the same valve assembly in compressed position after a dose in which the valve stem has been depressed.

FIG. 5 is a second configuration in which the actuating button fits into a movable applicator nozzle for storage.

As shown in FIG. 1, the biggest element of the aerosol dispenser is the deceleration chamber 11, preferably of a plastic such as polyethylene. The deceleration chamber has a cylindrical barrel 12 which conveniently may be about $2\frac{3}{4}$ inches in length and $1\frac{1}{2}$ inches in internal diameter with a shell wall thickness of around one sixteenth inch. At one end is a mouthpiece 13 conveniently about seven eighths inch in outside diameter and five-eighths inch long which is a size conveniently held in the lips of the user with the lips forming an essentially airtight seal with the mouthpiece. The mouthpiece is joined to the cylindrical barrel 12 by a chamber-to-mouthpiece flare 14. Conveniently, but not necessarily, the mouthpiece, the chamber-to-mouthpiece flare, and the cylindrical barrel are molded in one piece from a plastic such as linear polyethylene. This gives an economical method of manufacture and a smooth, easily cleanable working surface. A mouthpiece cap 15 fits removably on the mouthpiece in dust excluding relationship. The cap may slide on either interiorly or exteriorly with a finger friction fit. The term "finger friction fit" is used to note a frictional relationship which will hold pieces together under normal handling conditions, but may be readily disengaged or engaged by finger pressure only. The exterior surface of the mouthpiece cap may be roughened or knurled for easier grasping by

the fingers. The edges of the mouthpiece cap and the mouthpiece may be "broken" or slightly rounded in accordance with conventional practice for ease in assembly, as may other edges. Either the mouthpiece or the mouthpiece cap may have small ribs of the order of 0.002 inch to reduce friction and ease engagement. By having such small raised portions or beads on frictionally engaging portions, the natural resilience of plastic such as polyethylene is utilized to give a frictional engagement which may be readily disengaged with the fingers without expensive requirements as to accuracy in sizing of the pieces. Similar assembly details may be used elsewhere in the present dispenser, and are conventional in the plastics molding art.

At the open end of the cylindrical barrel 12 is a container holder 16. The container holder is a multifunctional element. A holder flange 17 fits across the open end of the cylindrical barrel 12. A positioning sleeve 18 engages the end of the cylindrical barrel 12. Conveniently, but not necessarily, the positioning sleeve fits interiorly of the cylindrical barrel 12 with a friction fit and the positioning sleeve is long enough to prevent accidental disengagement but permit ready removal of the container holder 16. Conveniently, but not necessarily, the positioning sleeve 18 extends from the holder flange 17 so that its resilience permits finger frictional engagement with the normal accuracy of molding parts. A container holding sleeve 19 extends interiorly from the holder flange 17 and is of a size to fit around, retain, and position an aerosol container 20. Conveniently, but not necessarily, the aerosol container 20 is of stainless steel or aluminum to hold high pressure aerosol propellants. The container holding sleeve is long enough and of a size to position and retain the aerosol container assembly inside and axially of the deceleration chamber 11 during storage and transportation phases of using the device, and permits ready disengagement from the aerosol container 20 at the time of administration.

Through the holder flange extend one or more air vents 21 which provide for the introduction of diluent air during use. Three vents, each one eighth inch diameter, give good results.

Extending exteriorly from the holder flange 17 is a button holder 22. The button holder is hollow, has a closed end opposite to the holder flange, and has therein an indexing port 23 which is of a size and shape to hold an aerosol actuating button 24, which is described in more detail below. Because the aerosol actuating button is to be oriented, the shape of the indexing port 23 is such as to match with the actuating button 24 and hold the actuating button in an oriented relationship. As shown, the actuating button is cylindrical with a flat side 25 which flat side cooperates with an indexing port flat 26 so that the spray is directed axially of the deceleration chamber. Conveniently, but not necessarily, the button holder is formed with two indexing ports 23 in diametrically opposed relationship so that the actuating button 24 can be inserted from either side and the other port serves such as an additional air inlet. At the end of the button holder 22 away from the holder flange 17 is a retaining bead 27 which conveniently extends up about five one thousandths of an inch above the exterior cylindrical surface of the button holder. A protective sleeve 28 fits in light frictional engagement over and on the exterior surface of the button holder. Being made of plastic, there is sufficient re-

silience that the protective sleeve 28 may be easily forced over the retaining bead 27 into position and is not readily removed so that it is retained in place during the useful life of the dispenser. The protective sleeve has button apertures 29 to permit the sleeve 28 to be rotated so that the button apertures 29 index with the indexing ports and permit the button to be inserted therethrough and yet can be rotated through about 90° to protect the assembly from the entrance of dust and dirt during storage and transportation.

In FIG. 2 is shown the dispenser in the carrying configuration for storage and transportation in which the aerosol container 20 is held in the container holding sleeve 19 interiorly of the cylindrical barrel of the deceleration chamber.

The aerosol container 20 is closed with a valve assembly 30 which includes a ferrule 31 to hold the valve in position and from which valve assembly extends the actuating button 24.

As shown in FIG. 3, at the time of use, the mouth-piece cap 15 is removed, the holder flange 17 removed from the other end of the cylindrical barrel, the aerosol container 20 is removed from the container holding sleeve 19, the protective sleeve 28 rotated until the button apertures 29 index with the indexing port 23, and assembled in dose administering configuration by inserting the actuating button 24 through the button aperture 29 into one of the indexing ports 13 so that the spray port 32 is axial and concentric with the cylindrical barrel 12 of the deceleration chamber, so that the discharge from the aerosol container is symmetrical with respect to the deceleration chamber.

As shown in FIG. 3, in the dose administering position the aerosol container 20 extends upwards so that the medicament in propellant 33 is drawn by gravity against the valve assembly 30.

The actuating button 24 has a spray port 32 which is conveniently counterbored into the button and has a spray orifice 34 through which the medicament in propellant is discharged. This spray orifice may either be formed integral with the spray button or a separate metallic insert may be used. Both are conventional constructions. The spray orifice should have a diameter such that the discharged dose is dispersed in finely divided form as a cone on exit from the spray orifice.

An orifice of about 0.015 to 0.018 inch gives a good spray pattern.

The actuating button 24 fits snugly on the end of a valve stem 35 which extends into the valve body 36. The valve body 36 has therein a metering chamber 37 in which the valve stem 35 is slidably mounted. Between the valve body and the ferrule 31 is a metering gasket 38 which performs the dual function of serving as a seal against loss of propellant when the valve stem collar 39 presses against the metering gasket, and acts as a ring seal around the valve stem 35 so that as the valve stem is depressed against the valve spring 40, the metering port 41 in the valve stem passes the metering gasket and permits the contents of the metering chamber to pass through the metering port 41, the axial valve stem bore 42, extending through the valve stem, into the discharge passage 43 in the actuating button 24 to the spray orifice 34. At the inner end of the valve stem 35 are charging flutes 44. These cooperate with a charging gasket 45 which is held against the lower end of the metering chamber by a stainless steel valve stem washer 46 which, in turn, is held against the bot-

ton of the metering chamber 37 by the valve spring 40. In operation, as the valve stem 35 is depressed, the valve stem 35 passes through the charging gasket 45 so that the charging flutes pass through the charging gasket and the full diameter of the valve stem 35 seals against the charging gasket 45 so that the metering chamber is filled and closed at the inner end before the metering port 41 passes the metering gasket 38 which permits the contents of the metering chamber to discharge through the metering port 41, the axial valve stem bore 42, the discharge passage 43, and the spray orifice 34.

FIG. 4 shows the actuating button 24 in depressed position with the valve in the discharge position.

When pressure on the actuating button 24 is released, the valve stem 35 is pushed outwardly by the valve spring 40 so that the metering port 41 passes the metering gasket 38 which closes discharge from the metering chamber, and later the charging flutes 44 pass the charging gasket 45 permitting the propellant containing the medicament to flow through the charging flutes 44 and again fill the metering chamber 37.

The valve body 36 has a valve body flange 47 which covers the end of the aerosol container 20 and is sealed thereto by a container gasket 48. The ferrule 31 holds the assembly in position against the end of the aerosol container 20 by the ferrule 31 being swaged against the stainless steel or aluminum aerosol container 20.

The above construction for a metering valve is one type of metering valve. Other conventional types of metering valves may be used.

Because the metering valve discharges a comparatively small charge, for instance about 50 microliters per actuation is a convenient commercial size, and each discharge has a volume of about that of a small drop of water, it is important that the metering chamber be completely filled before each actuation and that the metering chamber be prevented from draining back into the aerosol container between actuations. This loss of charge or loss of prime is prevented by an anti-drain tank 49. The anti-drain tank 49 fits into a flange sleeve 50 on the valve body flange 47 which flange sleeve 50 has an interior cylindrical surface against which the anti-drain tank 49 is a snug friction fit. In the periphery of the anti-drain tank 49 and between the anti-drain tank and the flange sleeve 50 is a charging passage 51 which provides for refilling of the anti-drain tank from the main body of the medicament in propellant in the aerosol container.

To protect against accidental disengagement of the anti-drain tank as, for example, by dropping the aerosol container on the floor during use, the anti-drain tank is sonically welded into position using an ultrasonic seal in which ultrasonic energy is passed through the flange sleeve to the anti-drain tank. As the energy passes through, there is a discontinuity between the anti-drain tank and the flange sleeve so that energy is reflected and refracted causing dissipation of ultrasonic energy which reappears as heat which melts and thereby seals the anti-drain tank to the flange sleeve. By such ultrasonic sealing, the assembly is economical and effective. When so sealed, the anti-drain tank remains in position under any use or abuse that does not damage the aerosol container itself.

Because of the nature of the propellant composition, when the actuating button is depressed with the aerosol container in dispensing position, the contents of the

metering chamber are discharged and as the actuating button is released, a new charge is drawn from the anti-drain tank into the metering chamber and the anti-drain tank is refilled through the charging passage 51. The anti-drain tank remains filled with the propellant containing the medicament independent of the orientation of the aerosol container. Thus, a predictable, uniform, accurate dosage is dispensed with each actuation of the actuating button.

By keeping the fluted end of the valve stem immersed in liquid propellant at all times, the homogeneity of the solid finely divided medicament in the propellant is maintained more uniformly, and more consistent uniform doses are dispersed. The use of a plastic anti-drain tank appears to aid in neutralizing electrical charges which would otherwise build up in the system. With a stainless steel aerosol container 20, the periphery of the propellant charge is effectively at a single potential, but the propellant can act as a dielectric so that the individual particles of triamcinolone acetonide become charged and affect their dispersion and discharge rate. With the anti-drain tank, the effect of the stainless steel container is at least in part neutralized so that static effects are reduced or minimized permitting more uniform charge characteristics.

In the absence of the anti-drain tank, the first twenty-five percent of discharge doses are found to be higher than the last twenty-five percent so that the user is receiving more triamcinolone acetonide than anticipated from the new dispenser and less than anticipated from the nearly empty dispenser. With the present anti-drain tank, the variation in charges are minimized so that the user is obtaining a more reliably uniform dosage of triamcinolone acetonide.

It is difficult to measure the effect of electrical charges within the aerosol container and in the deceleration chamber but independent of the theoretical and scientific background for explaining uniformity of charge, it is found that with the present anti-drain tank, more uniform dosages are dispensed and with the deceleration chamber in which the mouthpiece has less than half the cross sectional area of the cylindrical barrel, and the length of the cylindrical barrel is less than twice its diameter, the individual dosages of triamcinolone acetonide in propellant are dispersed into the deceleration chamber and lose the jet velocity imparted by the propellant spray. If any particles still retain velocity, they either impinge or are retained by the walls of the deceleration chamber or are bounced away from the walls so that a dispersed powder charge is formed which is mixed with additional diluent air and inhaled, as the user inhales the finely divided triamcinolone acetonide through the mouthpiece. A large portion of the triamcinolone acetonide which would otherwise be deposited in the mouth of the user and, hence, absorbed systemically, are deposited on the walls of the deceleration chamber.

Even though the triamcinolone acetonide is fairly expensive, the dosages are so small that about a 25 to 50% loss in the deceleration chamber is a highly acceptable loss as compared with the advantages of consistency and uniformity of the dose which is administered to the patient. Uniformity is important so that the physician administering knows what adjustments in dosage level need be made depending on the response of the user.

In FIG. 5 is shown a modification of the aerosol dispenser system in which the container holding sleeve of the type shown in Meshberg, U.S. Pat. No. 3,012,555, supra, is used with an applicator nozzle 52 fitting in the holder flange 53 with the bottom end of the aerosol container fitting into the applicator nozzle. Slidably fitting in the other end of the applicator nozzle is a button holding slide 54 which can be pressed inward for sealing or pulled outward to hold the actuating button in operating position. The details of this construction are shown in said U.S. Pat. No. 3,012,555.

With a metering trap holding about 50 microliters of material, the energy of discharge is completely dissipated in the deceleration trap and a fine aerosol, almost a smoke, is formed.

For Applicant's purpose, a particle size range from about 0.5 microns to 10 microns gives good results. Particles larger than about 10 microns are too apt to be deposited in the mouth or the throat of the user to be preferred for inhalation therapy. A few particles in this size range are usually not deleterious, but contribute disproportionately to systemic absorption rather than through the lungs.

In use, because part of the triamcinolone acetonide deposits on the walls of the deceleration chamber, the chamber should be washed occasionally.

To insure adequate dispersion of the powdered triamcinolone acetonide, a comparatively high pressure propellant system is preferred. Dichlorodifluoromethane (Freon 12) which has a pressure of about 80 pounds per square inch absolute at room temperature gives good results. A stainless steel or aluminum container is preferred for such pressures to avoid damage from breakage. Glass containers, or plastic containers, or a plastic covered and protected glass container may be used, but these are more conventional at lower pressures, of the order of 30 to 50 pounds per square inch gage.

A plastic valve stem is preferred to metal, as the plastic valve stem is less subject to binding or sticking from powder being packed around it. A small amount of alcohol, about 1 to 10%, functions as a lubricant to keep valve action reliable.

Obviously, the size of the container and the size of the metering chamber can vary widely depending upon the dosage desired per actuation, and the number of actuations desired in the dispenser.

Example I

Triamcinolone acetonide aerosol

Triamcinolone acetonide was micronized in a fluid energy mill until 90% by weight was in the particle size range of 1 to 5 microns.

A 19 ml. stainless steel container had charged thereto 30 mg. of the micronized triamcinolone acetonide, 0.244 ml. of anhydrous ethanol and was cold filled with 19.5 grams of dichlorodifluoromethane at -40°C, evaporation serving to chill the container, and an excess being added to allow for evaporation. The filled containers were closed with a metering valve, as above described, and sealed. Dispersion in the propellant is improved when the filled containers are immersed in an ultrasonic bath that transfers energy from the transducer to the contents of the aerosol container.

Good results are normally obtained by shaking to disperse the triamcinolone acetonide in the system. Ultrasonic dispersal is preferred to insure more uniform dis-

persion in micronized form, and reduce the number of aggregates.

The components can be mixed, treated ultrasonically, and pressure filled. Pressure filling is more complex for small scale runs, but often preferred for large size runs, and saves loss of the propellant. The valve needs to be specifically designed for such pressure fill.

Each actuation of the valve button delivers about 0.1 mg. of triamcinolone acetonide. Five actuations four times a day gives a dosage of about 2 mg. of triamcinolone acetonide. As a portion is retained in the deceleration chamber, and some is exhaled, slightly more than 1 mg. a day is administered for a typical patient. A systemic dose for a patient is about 8 mg. The lower level and delivery to the preferred site is a major advantage.

The patient should hold inspired triamcinolone acetonide for a few seconds to permit the particles to contact the walls of the air-sacs and passages deep in the lungs.

Example II

A suspension was prepared of:

Example II

A suspension was prepared of:

Triamcinolone acetonide, micronized (0.5-5 microns)	400 mg.
Dichlorodifluoromethane	100 ml.
Sorbitan trioleate	6.9 mg.

The triamcinolone acetonide and sorbitan trioleate were placed in a beaker, and the dichlorodifluoromethane was added at -40°C. A suspension was formed. The mixture was sonified, that is, treated with a Sonifier, manufactured by the Branson Sonic Power Co., Eagle Road, Danbury, Connecticut, as model LS75 at a current input of 9 amperes for 2 minutes. Additional cold dichlorodifluoromethane was added as necessary to keep the volume at 100 ml. The mixture was uniformly dispersed, and had increased stability re-

sulting from the sonification.

19 cc stainless steel containers were filled with 15 ml. of the cold mixture, valves as described above inserted and the valves sealed in place.

On warming, after storage, the triamcinolone acetonide remained dispersed, and after merely casual shaking, gave uniform doses of finely divided triamcinolone acetonide.

Good results are obtained on inhalation by asthmatics.

Example III

The procedure of Example II was repeated substituting 1.24 ml. of anhydrous ethanol for the sorbitan trioleate. The suspension was stable on filling and on storage. Shaking to uniformly disperse before using is recommended.

The dispenser gave comparatively uniform doses from the initial actuation until empty. Five actuations four times a day, for a total of about 2 mg. of triamcinolone acetonide per patient is recommended as an initial program, with the dose rate subject to adjustment based on clinical results in a particular patient.

I claim:

1. A method of treating asthma which comprises dispensing a measured dose through a metering valve into a deceleration chamber of a suspension in a chlorofluoroalkane propellant of finely divided triamcinolone acetonide having 95% by weight within the particle size range of about 0.5 to 10 microns, the individual particles of which are substantially separated, mixing with additional air, and inhaling, by inspirational air velocity only, into the lungs of the subject, holding the inspired air for a short time to permit a substantial portion of the particles of triamcinolone acetonide to be deposited along the lung surface, and exhaling.

* * * * *