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[54] DYNAMIC PARTICLE SIZE CONTROL FOR AEROSOLIZED DRUG DELIVERY

5,063,921 11/1991 Howe 128/200.14

(List continued on next page.)

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FOREIGN PATENT DOCUMENTS

0546607	6/1993	European Pat. Off. .	
0572969	12/1993	European Pat. Off. .	
764682	9/1980	U.S.S.R.	128/203.27
1353440	11/1987	U.S.S.R.	128/200.18
85/00112	1/1985	WIPO	128/203.27
WO92/15353	9/1992	WIPO .	
WO93/12823	7/1993	WIPO .	
WO93/17728	9/1993	WIPO .	

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OTHER PUBLICATIONS

Newman, Stephen P., "Deposition and Effects of Inhalation Aerosols," Rahms i Lund Tryckeri AB, 1983, pp. 1-113.

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[56] References Cited

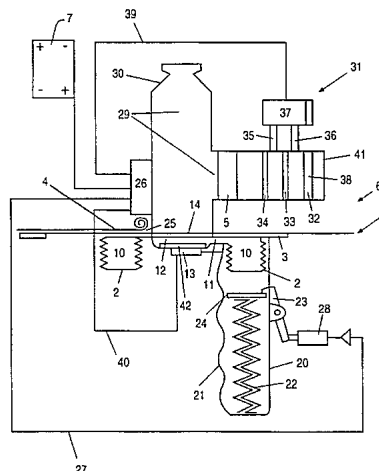
U.S. PATENT DOCUMENTS

3,157,179	11/1964	Paullus et al.	128/211
3,187,748	6/1965	Mitchell et al.	128/173
3,456,646	7/1969	Phillips et al.	128/173
3,565,070	2/1971	Hanson et al.	128/173
3,812,854	5/1974	Michaels et al.	128/194
3,826,413	7/1974	Warren	222/402.13
3,861,386	1/1975	Harris et al.	128/194
3,948,264	4/1976	Wilke et al.	128/203.15
3,991,304	11/1976	Hillsman	235/151.34
4,256,017	3/1981	Eastman	91/417
4,274,403	6/1981	Struve	128/203.15
4,524,769	6/1985	Wetterlin	128/203.15
4,533,082	8/1985	Maehara et al.	239/102
4,564,748	1/1986	Gupton	219/497
4,627,432	12/1986	Newell et al.	128/203.15
4,649,911	3/1987	Knight et al.	128/200.21
4,699,136	10/1987	Krauser	128/203.72
4,832,012	5/1989	Raabe et al.	128/200.21
4,877,989	10/1989	Drews et al.	310/323
4,922,901	5/1990	Brooks et al.	128/203.26
4,963,327	10/1990	Russell	422/120
5,042,472	8/1991	Bunin	128/203.15

[57] ABSTRACT

A device is provided which creates aerosolized particles by forcing a formulation of drug in a carrier through a nozzle (which nozzle may be in the form of a porous membrane) into a channel to a patient for inhalation. While in the channel energy is added to the particles in an amount sufficient to evaporate carrier and thereby reduce particle size. The amount of energy added can be adjusted depending on factors such as the particle size, the amount of the carrier to be evaporated, the water vapor content of the surrounding air and the composition of the carrier. Energy may be added in an amount sufficient to evaporate all carrier and thereby provide particles of dry powdered drug to patient which particles are uniform in size regardless of the surrounding humidity and smaller due to the evaporation of the carrier. Air drawn into the device by the patient may be drawn through a desiccator containing a desiccant which removes moisture from the air thereby improving evaporation efficiency when the carrier is water. Alternatively, water vapor may be introduced to the channel to saturate inhaled air thereby preventing evaporation of carrier and maintaining uniform particle size.

18 Claims, 3 Drawing Sheets



U.S. PATENT DOCUMENTS			
5,152,456	10/1992	Ross et al.	128/203.26
5,156,776	10/1992	Loedding et al.	261/27
5,186,164	2/1993	Raghuprasad	128/200.14
5,201,308	4/1993	Newhouse	128/203.15
5,327,883	7/1994	Williams et al.	128/203.12
5,372,148	12/1994	McCafferty	131/194
5,383,850	1/1995	Schwab et al.	604/58
5,396,884	3/1995	Bagwell et al.	128/200.21
5,404,871	4/1995	Goodman et al.	128/200.14

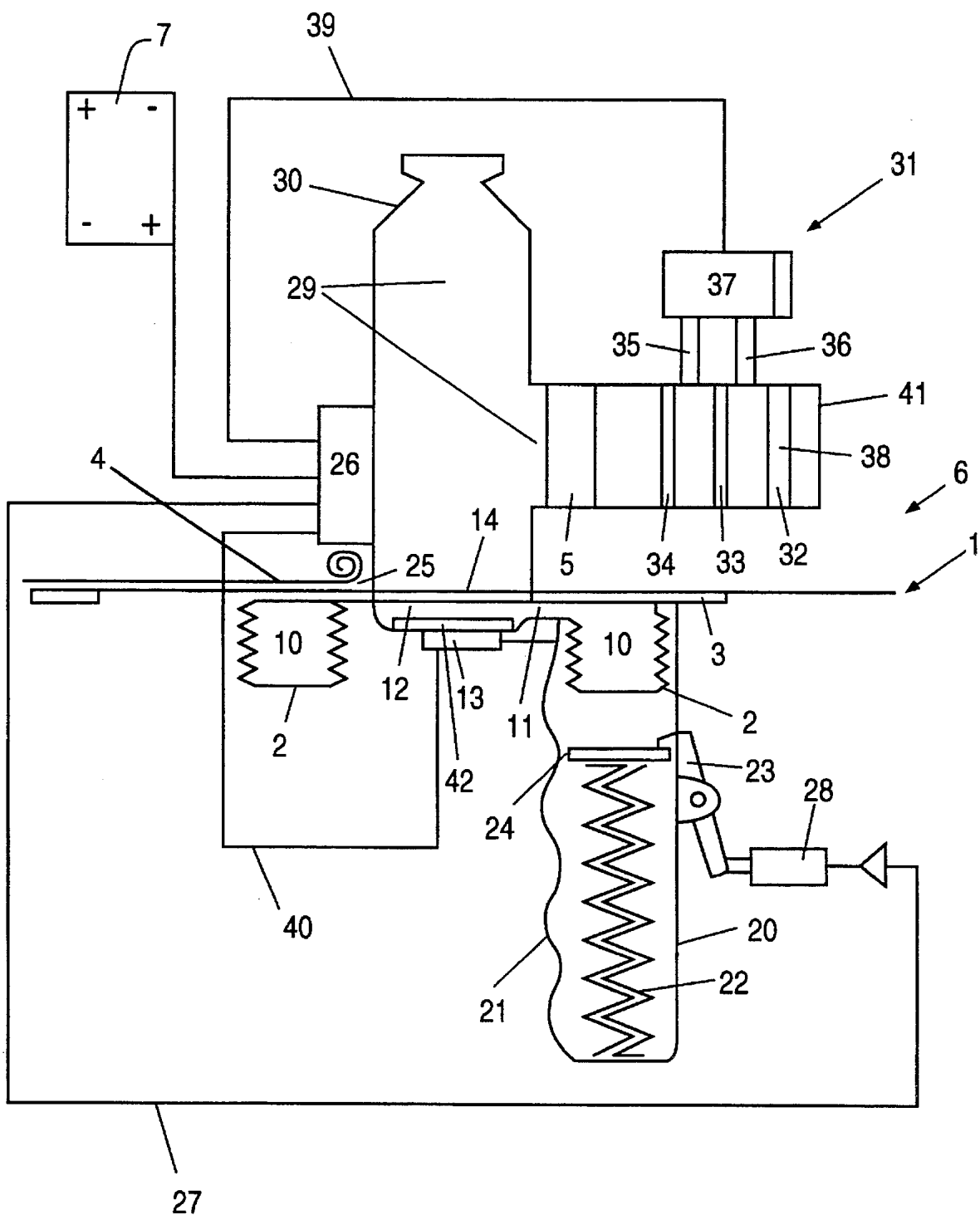


FIG. 1

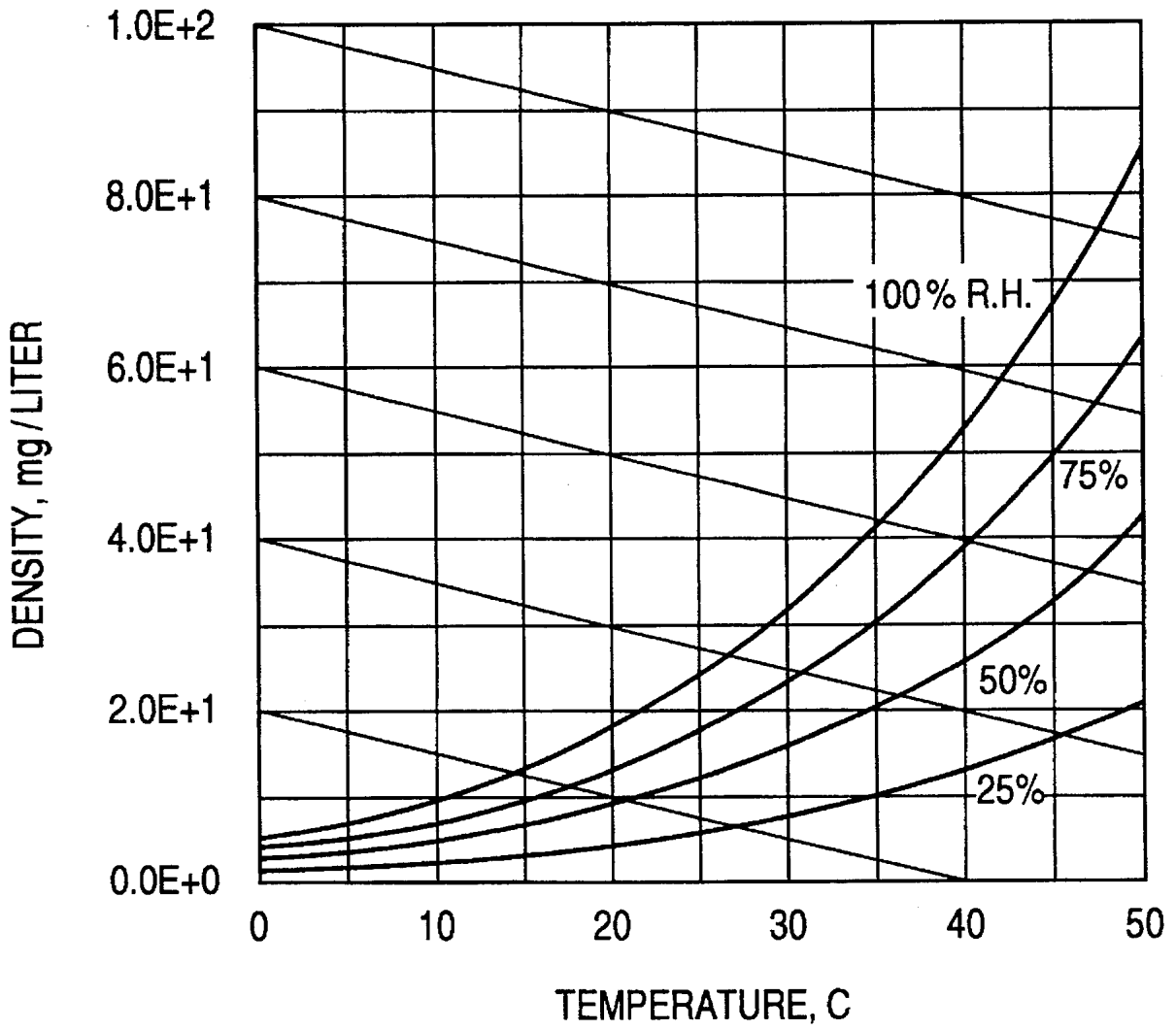


FIG. 2

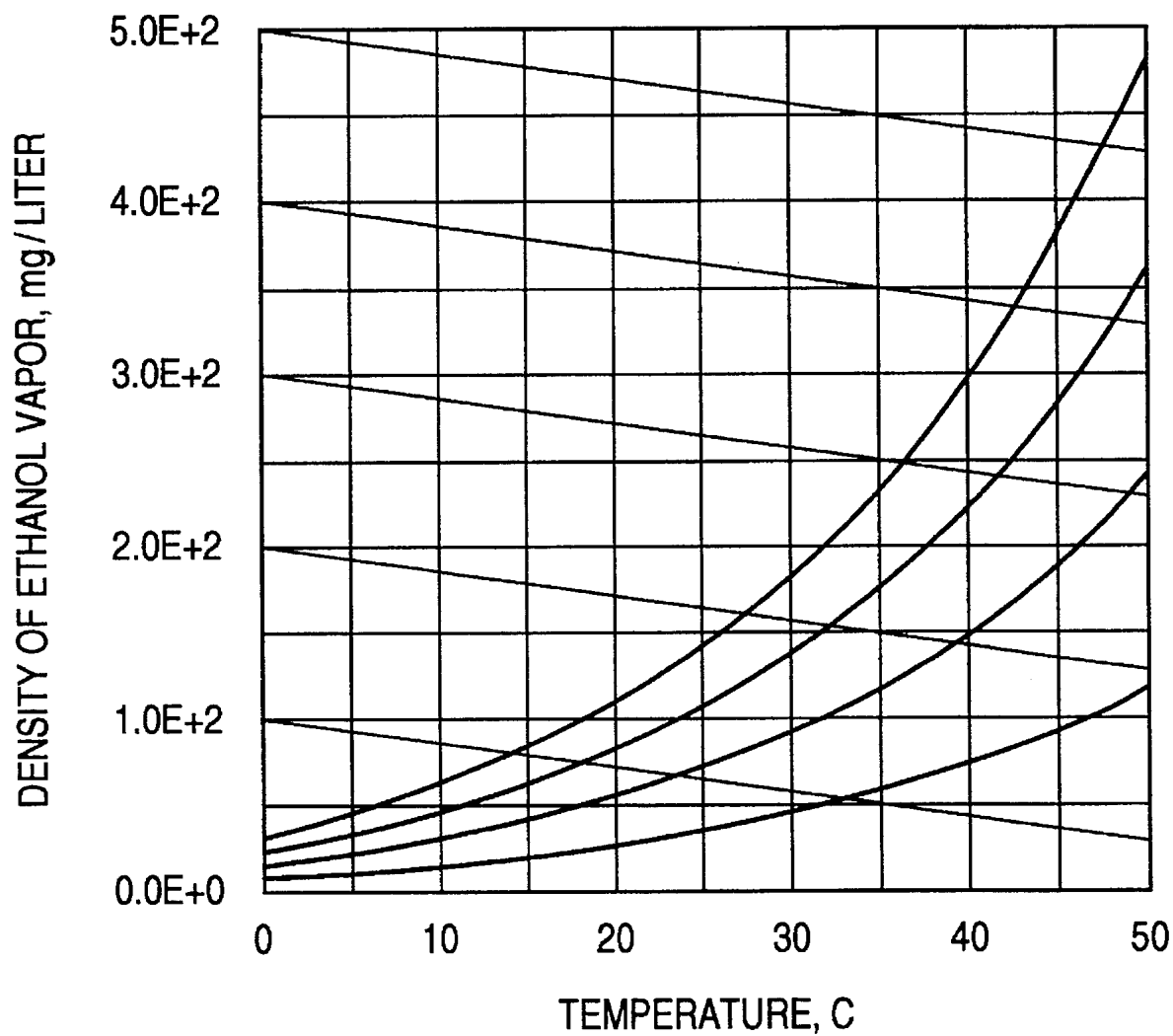


FIG. 3

DYNAMIC PARTICLE SIZE CONTROL FOR AEROSOLIZED DRUG DELIVERY

FIELD OF THE INVENTION

This invention relates generally to the field of methods and devices for the delivery of pharmaceutically active drugs. More specifically, the invention relates to methods and devices for the delivery of aerosolized drug formulations.

BACKGROUND OF THE INVENTION

The intrapulmonary delivery of pharmaceutically active drugs is accomplished by a number of distinct methodologies. In accordance with one method, a pharmaceutically active drug is dispersed in a low boiling point propellant (a CFC or HFA) and loaded in a pressurized canister from which the drug/propellant formulation may be released by the use of a device generally known as a metered dose inhaler (MDI). Once released, the propellant evaporates and particles of the drug are inhaled by the patient. Another method involves the use of a nebulizer which creates a mist of fine particles from a solution or suspension of a drug which mist is inhaled through the mouth and/or nose by the patient. In yet another method of dry powered drug (which may be included in packets) are inhaled. These methods are hindered by significant problems relating to patient compliance and dosing as described further below.

The use of dry powders in systems presents some unique difficulties. Firstly, the dry powders are difficult to store and can be easily contaminated with water vapors causing the powders to clump together. Systems which do not include dry powders include the drug dissolved or suspended in a liquid carrier. Although there are advantages to these systems (e.g., avoiding the clumping of powder particles) these systems are also affected by moisture in the surrounding air, i.e. humidity. Specifically, such systems may use water as the carrier, i.e. a formulation comprised of a drug and water is used to create aerosolized particles. The carrier such as the water in the particles evaporates after the particles are formed. However, the rate and amount of evaporation can vary if the surrounding humidity varies. The amount of evaporation effects the particle size which effects the amount of particles which reach the lung and the particular area of the lung which the particles can reach. Several aspects of the present invention are directed at eliminating the variability in particle size due to surrounding humidity. Other devices known for intrapulmonary drug delivery are discussed below as are some of the advantages and disadvantages of these devices.

Metered dose inhalers that are generally manually operated and some breath actuated devices have been proposed and produced. Breath actuated inhalers typically contain a pressurized propellant and provide a metered dose automatically when the patient's inspiratory effort either moves a mechanical lever or the detected flow rises above a preset threshold, as detected by a hot wire anemometer. See, for example, U.S. Pat. Nos. 3,187,748; 3,565,070; 3,814,297; 3,826,413; 4,592,348; 4,648,393; 4,803,978; 4,896,832; and a product available from 3M Healthcare known as Aerosol Sheathed Actuator and Cap.

A major problem with manual metered dose inhalers is that the patient frequently actuates the device at the incorrect point during the breathing cycle to obtain the benefits of the intended drug therapy or breathes at the wrong flow rate. Thus, patients may inspire too little medication, or take

additional doses and receive too much medication or deliver the drug to the throat or mouth rather than the lung. The problem is, therefore, the inability to administer precise dosages.

A problem with breath activated drug delivery is that the dose is triggered on crossing a fixed threshold inspiratory effort. Thus, an inspiration effort may be sufficient to release a metered dose, but the inspiratory flow following the release may not be sufficient to cause the aerosol medication to pass into the desired portion of the patient's airways. Another problem exists with patients whose inspiratory effort is not sufficient to rise above the threshold to trigger the release valve at all. Yet another problem is that the velocity and size of the particles released can vary greatly.

Attempts have been made to solve the patient inspiration synchronization problem. U.S. Pat. No. 4,484,577 refers to using a bidirectional reed whistle to indicate to the patient the maximum rate of inhalation for desired delivery of the drug and flow restrictor to prevent the patient from inhaling too rapidly. U.S. Pat. No. 3,991,304 refers to using biofeedback techniques to train the patient to adopt a desired breathing pattern. U.S. Pat. No. 4,677,975 refers to using audible signals and preselected time delays gated on the detection of inspiratory flow to indicate to the patient when to inhale and exhale, and delivering inhalable material a selected time after the detected onset of flow.

Studies in Byron (ed.), *Respiratory Drug Delivery*, CRC Press, Inc. (1990); Newman et al., *Thorax*, 1981, 36:52-55; Newman et al., *Thorax*, 1980, 35:234; Newman et al., *Eur. J. Respir. Dis.*, 1981, 62:3-21; and Newman et al., *Am. Rev. Respir. Dis.*, 1981, 124:317-320 indicate that during a single breath of an aerosol compound, only about ten percent of the total aerosol material presented is deposited into the lungs and that the location of deposition in the lung depends upon (1) breath parameters such as volume of inspiration, inspiratory flow rate, breath holding prior to expiration, the lung volume at the time the bolus of medication is administered, and expiratory flow rate, (2) the size, shape and density of the aerosol particles (i.e., the medicinal compound, any carrier, and propellant), and (3) the physiological characteristics of the patient. Present devices and methods cannot eliminate these variables and as such cannot control dosage administration.

A problem with existing metered dose inhalers, whether or not breath actuated, is that they are factory preset to deliver a fixed dose at a given particle size distribution. Such devices are not capable of reducing the dose to reflect improvement in the patient's condition, or selecting a maximum desired respirable fraction of the aerosol mist that is suitable for a desired location of delivery of the medication in the particular patient.

Devices for controlling particle size of an aerosol are known. U.S. Pat. No. 4,790,305 refers to controlling the particle size of a metered dose of aerosol for delivery to the walls of small bronchi and bronchioles by filling a first chamber with medication and a second chamber with air such that all of the air is inhaled prior to the inhaling medication, and using flow control orifices to control the flow rate. U.S. Pat. No. 4,926,852 refers to metering a dose of medication into a flow-through chamber that has orifices to limit the flow rate to control particle size. U.S. Pat. No. 4,677,975 refers to a nebulizer device that uses baffles to remove from any aerosol particles above a selected size. U.S. Pat. No. 3,658,059 refers to a baffle that changes the size of an aperture in the passage of the suspension being inhaled to select the quantity and size of suspended particles

delivered. A problem with these devices is that they process the aerosol after it is generated and thus are inefficient.

It is well known that pulmonary functions, such as forced expiratory volume in one second, forced vital capacity, and peak expiratory flow rate, can be measured using flow rates and used to (1) diagnose the existence of medical conditions, (2) prescribe medication, and (3) ascertain the efficiency of a drug therapy program. See, for example, U.S. Pat. Nos. 3,991,304 and 4,852,582 and the publications of Newman et al. discussed above wherein volume but not flow rate is measured to determine the point of drug release which is preferred for maximizing the delivery of the drug. Heretofore, these tests have been performed using available spirometers. U.S. Pat. No. 4,852,582 also refers to using a peak flow rate meter to measure changes in peak flow rate before and after administration of a bronchodilator. The results of such tests before and after administration of several different medications are used to evaluate the efficiency of the medications.

Some devices only measure pulmonary function and do not deliver drugs. Devices which do deliver drugs are often too complicated for most patients to use effectively and obtain repeated delivery of a given amount of drug i.e. user error in administration causes significant variability in the amount of drug the patient receives. In other devices the data obtained does not directly effect the operation of the device, i.e. it must be examined and interpreted by a trained medical practitioner to be meaningful.

Attempts have been made to solve many of the above-referred-to problems. However, inconsistent user compliance combined with undesirably large and variable particle size continues to cause problems with obtaining precise dosing.

Nebulizers utilize various means in order to create a fog or mist from an aqueous solution or suspension containing a pharmaceutically active drug. The mist created by the nebulizer device is directed towards the face of the patient and inhaled through the mouth and nose. Nebulizer devices and methodology can be quite useful when the precise dosing of the drug being delivered to the patient is not of particular importance. For example, in some situations the nebulizer creates a mist from an aqueous solution containing a bronchodilator which can be inhaled by the patient until the patient feels some improvement in lung function. When precise dosing is more important the nebulizer device and delivery methodology suffers from many of the disadvantages of metered dose inhaler devices and methodology as described above. In addition, nebulizers are generally large in size and not hand-held, easily transportable devices like MDIs. Large nebulizers can only be used within a fixed location such as the patient's home, the doctor's office and/or hospital. However, a portable nebulizer is taught in published PCT application WO92/11050 incorporated herein by reference. Another nebulizer which uses a high frequency generator to create an aerosol is described in U.S. Pat. No. 3,812,854 issued May 28, 1974. Drug formulations placed in nebulizers are generally diluted prior to delivery. The entire diluted formulation must generally be administered at a single dosing event in order to maintain the desired level of sterility and the nebulizer must be cleaned after use. Yet another disadvantage of nebulizers is that they produce an aerosol which has a distribution of particle sizes not all of which are of appropriate size to reach the targeted areas of the lung. The present invention endeavors to address and solve these and other problems.

SUMMARY OF THE INVENTION

A device is provided which creates aerosolized particles by moving a formulation of drug in a carrier through a

nozzle (which nozzle may be in the form of a porous membrane) into a channel to a patient for inhalation. While in the channel energy is actively added to the particles in an amount sufficient to evaporate carrier and thereby reduce particle size. The air drawn into the device is actively heated by moving the air through a heating material which material is pre-heated prior to the beginning of a patient's inhalation. The amount of energy added can be adjusted depending on factors such as the desired particle size, the amount of the carrier to be evaporated, the water vapor content of the surrounding air and the composition of the carrier. Energy may be added in an amount sufficient to evaporate all or substantially all carrier and thereby provide particles of dry powdered drug or highly concentrated drug to patient which particles are uniform in size regardless of the surrounding humidity and smaller due to the evaporation of the carrier. Air drawn into the device by the patient may be drawn through a desiccator containing a desiccant which removes moisture from the air thereby improving evaporation efficiency when the carrier is water. Alternatively, water vapor or aerosolized water may be introduced to the channel to saturate inhaled air thereby preventing evaporation of carrier and maintaining particle size. By adding energy some or all carrier can be evaporated. Alternatively, by adding water evaporation can be prevented. Either procedure provides a desired result in that the size of the particles may be modified or maintained regardless of the surrounding humidity of the air where the device is used.

An object of the invention is to provide a drug delivery device which creates aerosolized particles of a formulation comprised of drug in a carrier and adds energy to the particles in an amount sufficient to evaporate carrier and reduce total particle size.

Another object is to provide a drug delivery device which includes a desiccator for drying air in a manner so as to remove water vapor.

Still another object is to provide a drug delivery device which includes a mechanism for adding water vapor to inhaled air so as to saturate the air and limit or prevent evaporation of carrier.

Yet another object is to provide a drug delivery device which makes it possible to add energy to a formulation prior to the creation of aerosolized particles, after the creation of aerosolized particles or at both times (either or both of which procedures may be carried out with the use of a desiccator for removing water vapor from the air).

A feature of the invention is that drug can be dispersed or dissolved in a liquid carrier such as water and dispersed to a patient as dry or almost dry particles.

An advantage of the invention is that particle size can be adjusted by adjusting the amount of energy added and thus the amount of evaporation obtained.

Another advantage is that the size of the particles delivered will be independent of the surrounding humidity.

These and other objects, advantages and features of the present invention will become apparent to those persons skilled in the art upon reading the present disclosure and reviewing the figures forming a part hereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a plan view of a drug delivery device of the invention;

FIG. 2 is a graph plotting the density of water vapor in air versus temperature; and

FIG. 3 is a graph plotting the density of ethanol vapor in air versus temperature.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Before the device and methodology of the present invention is described, it is to be understood that this invention is not limited to the particular packages, devices, systems, components, and formulations described, as such may, of course, vary. It is also to be understood that the terminology used herein is with the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe and disclose specific information for which the reference was cited in connection with.

Definitions

The term "velocity of the drug" shall mean the average speed of particles moving from a drug release point such as a valve to a patient's mouth.

The term "dosing event" shall be interpreted to mean the administration of a pharmaceutically active drug to a patient in need thereof by the intrapulmonary route of administration which event involves the release of drug into the inspiratory flow path of a patient. Accordingly, a dosing event may include the release of drug contained within one or more containers. A dosing event is not interrupted by a monitoring event which would indicate, if followed by further drug delivery, the beginning of a new dosing event.

The term "carrier" shall mean a liquid, flowable, pharmaceutically acceptable excipient material which a drug is suspended in or more preferably dissolved in. Useful carriers do not adversely interact with the drug. Preferred carriers include water, ethanol and mixtures thereof. Other carriers can be used provided that they can be formulated to create a suitable aerosol and do not adversely effect the drug or human lung tissue.

The term "measuring" describes an event whereby both the inspiratory flow rate and inspiratory volume of the patient is measured in order to determine an optimal point in the inspiratory cycle at which to release aerosolized drug. It is also preferable to continue measuring inspiratory flow during and after any drug delivery and to record inspiratory flow rate and volume before, during and after the release of drug. Such reading makes it possible to determine if drug was properly delivered to the patient.

The term "monitoring" event shall mean measuring lung functions such as inspiratory flow rate, and/or inspiratory volume so that a patient's lung function as defined herein, can be evaluated before and/or after drug delivery thereby making it possible to evaluate the efficiency of any treatment.

The term "inspiratory flow rate" shall mean a value of air flow calculated based on the speed of the air passing a given

point in a measuring device assuming atmospheric pressure $\pm 5\%$ and a temperature in the range of about 10°C . to 40°C .

The term "inspiratory flow" shall be interpreted to mean a value of air flow calculated based on the speed of the air passing a given point along with the volume of the air that has passed that point with the volume calculation being based on integration of the flow rate data and assuming atmospheric pressure, $\pm 5\%$ and temperature in the range of about 10°C . to about 40°C .

The term "inspiratory flow profile" shall be interpreted to mean data calculated in one or more events measuring inspiratory flow and cumulative volume, which profile can be used to determine a point within a patient's inspiratory cycle which is optimal for the release of drug to be delivered to a patient. An optimal point within the inspiratory cycle for the release of drug is based, in part, on a point within the inspiratory cycle likely to result in the maximum delivery of drug and based, in part, on a point in the cycle most likely to result in the delivery of a reproducible amount of drug to the patient at each release of drug. Repeatability of the amount delivered is the primary criterion and maximizing the amount delivered is an important but secondary criterion. Thus, a large number of different drug release points might be selected and provide for repeatability in dosing provided the selected point is again selected for subsequent releases. To insure maximum drug delivery the point is selected within given parameters.

The term "respiratory drug" shall be interpreted to mean any pharmaceutically effective compound used in the treatment of any respiratory disease and in particular the treatment of diseases such as asthma, bronchitis, emphysema and cystic fibrosis. Useful "respiratory drugs" include those which are listed within the Physician's Desk Reference (most recent edition). Such drugs include beta adrenergics which include bronchodilators including albuterol, isoproterenol sulfate, metaproterenol sulfate, terbutaline sulfate, pirbuterol acetate, salmeterol xinoatoate, formoterol; steroids including beclomethasone dipropionate, flunisolide, fluticasone, budesonide and triamcinolone acetonide. Anti-inflammatory drugs used in connection with the treatment of respiratory diseases include steroids such as beclomethasone dipropionate, triamcinolone acetonide, flunisolide and fluticasone. Other anti-inflammatory drugs include cromoglycates such as cromolyn sodium. Other respiratory drugs which would qualify as bronchodilators include anticholinergics including ipratropium bromide. The present invention is intended to encompass the free acids, free bases, salts, amines and various hydrate forms including semi-hydrate forms of such respiratory drugs and is particularly directed towards pharmaceutically acceptable formulations of such drugs which are formulated in combination with pharmaceutically acceptable excipient materials generally known to those skilled in the art—preferably without other additives such as preservatives. Preferred drug formulations do not include additional components which have a significant effect on the overall formulation such as preservatives. Thus preferred formulations consist essentially of pharmaceutically active drug and a pharmaceutically acceptable carrier (e.g., water and/or ethanol). However, if a drug is liquid without an excipient the formulation may consist essentially of the drug which has a sufficiently low viscosity that it can be aerosolized using a dispenser of the present invention.

The term "drug" shall include "respiratory drug" as well as other types of drugs such as systemically effective drugs. The term is intended to encompass the presently available pharmaceutically active drugs used therapeutically and to

further encompass to be developed therapeutically effective drugs which can be administered by the intrapulmonary route.

The term "therapeutic index" refers to the therapeutic index of a drug defined as LD_{50}/ED_{50} . The LD_{50} (lethal dose, 50%) is defined as the dose of a drug which kills 50% of the animals tested, and the ED_{50} is defined as the effective dose of the drug for 50% of the individuals treated. Drugs with a therapeutic index near unity (i.e. LD_{50}/ED_{50} is approximately equal to 1) achieve their therapeutic effect at doses very close to the toxic level and as such have a narrow therapeutic window, i.e. a narrow dose range over which they may be administered.

The terms "formulation" and "liquid formulation" and the like are used interchangeably herein to describe any pharmaceutically active drug with a pharmaceutically acceptable carrier in flowable liquid form. Such formulations are preferably solutions, e.g. aqueous solutions, ethanolic solutions, aqueous/ethanolic solutions, saline solutions and colloidal suspensions. Formulations can be solutions or suspensions of drug in a low boiling point propellant. Preferred formulations are drug(s) dissolved in water.

The terms "lung function" and "pulmonary function" are used interchangeably and shall be interpreted to mean physiologically measurable operations of a lung including but not limited to (1) inspiratory and (2) expiratory flow rates as well as (3) lung volume. Methods of quantitatively determining pulmonary function are used to measure lung function. Quantitative determination of pulmonary function is important because lung disease is typically associated with deteriorating pulmonary function. Methods of measuring pulmonary function most commonly employed in clinical practice involve timed measurement of inspiratory and expiratory maneuvers to measure specific parameters. For example, forced vital capacity (FVC) measures the total volume in liters exhaled by a patient forcefully from a deep initial inspiration. This parameter, when evaluated in conjunction with the forced expired volume in one second (FEV_1), allows bronchoconstriction to be quantitatively evaluated. A problem with forced vital capacity determination is that the forced vital capacity maneuver (i.e. forced exhalation from maximum inspiration to maximum expiration) is largely technique dependent. In other words, a given patient may produce different FVC values during a sequence of consecutive FVC maneuvers. The FEF_{25-75} or forced expiratory flow determined over the mid-portion of a forced exhalation maneuver tends to be less technique dependent than the FVC. Similarly, the FEV_1 tends to be less technique dependent than FVC. In addition to measuring volumes of exhaled air as indices of pulmonary function, the flow in liters per minute measured over differing portions of the expiratory cycle can be useful in determining the status of a patient's pulmonary function. In particular, the peak expiratory flow, taken as the highest air flow rate in liters per minute during a forced maximal exhalation, is well correlated with overall pulmonary function in a patient with asthma and other respiratory diseases. The present invention carries out treatment by administering drug in a drug delivery event and monitoring lung function in a monitoring event. A series of such events may be carried out and repeated over time to determine if lung function is improved.

Each of the parameters discussed above is measured during quantitative spirometry. A patient's individual performance can be compared against his personal best data, individual indices can be compared with each other for an individual patient (e.g. FEV_1 divided by FVC, producing a dimensionless index useful in assessing the severity of acute

asthma symptoms), or each of these indices can be compared against an expected value. Expected values for indices derived from quantitative spirometry are calculated as a function of the patient's sex, height, weight and age. For instance, standards exist for the calculation of expected indices and these are frequently reported along with the actual parameters derived for an individual patient during a monitoring event such as a quantitative spirometry test.

The term "substantially dry" shall mean that particles of formulation include an amount of carrier (e.g. water or ethanol) which is equal to (in weight) or less than the amount of drug in the particle.

The terms "particles" and "aerosolized particle" and the like are used interchangeably herein to mean small (1 to 25 μ in diameter) droplets of formulation which are temporarily suspended in air generally for the purpose of inhalation into a patient's lungs.

The term "respiratory disease" shall be interpreted to mean any pulmonary disease or impairment of lung function. Such diseases include restrictive and obstructive disease and diseases such as emphysema which involve abnormal distension of the lung frequently accompanied by impairment of heart action. Restrictive diseases tend to limit the total volume of air that a patient is able to exchange through inspiration and expiration. Restrictive disease, such as can be present in certain types of fibrotic processes, can therefore be detected by reduced FVC indices. Obstructive disease, such as is present in patients with asthma, tends not to affect the total volume of air exchangeable through inspiration and expiration but rather the amount of time required for forced exhalation of air. In particular, the FEV_1 is markedly reduced in patients with acute asthma symptoms. More specifically, the FEV_1 , when taken as a ratio of FVC (i.e. FEV_1 divided by FVC), is markedly reduced in patients with acute asthma. In addition to increasing the amount of time required for a full forced expiration, the presence of acute bronchoconstrictive disease tends to decrease the peak expiratory flow measured over a typical forced exhalation. The respiratory disease is understood to be "treated" if lung function is improved even if the improvement is temporary.

The terms "aerosolized particles" and "aerosolized particles of formulation" shall mean particles of formulation comprised of pharmaceutically active drug and carrier which are formed upon forcing the formulation through a nozzle which nozzle is preferably in the form of a porous membrane. The particles have a size which is sufficiently small such that when the particles are formed they remain suspended in the air for a sufficient amount of time such that the patient can inhale the particles into the patient's lungs. Preferably, the particles have a size in the range of 0.5 micron to about 12 microns having been created by being forced through the pores of a porous membrane which pores have a diameter in the range of about 0.25 micron to about 6.0 microns—the pores being present on the membrane in an amount of about ten to 10,000 pores over an area in size of from about 1 sq. millimeter to about 1 sq. centimeter.

Drug Delivery Device—With Disposable Package

A plan view showing some of the simple embodiments of a drug delivery device 6 of the present invention is shown within FIG. 1. This device operates with the disposable package 1. Before describing the details of the individual components of the device 6, a general description of the device and its operation is in order.

As indicated in the background of the invention, conventional metered dose inhalers and nebulizers suffer from a number of disadvantages. These disadvantages result in the inability to use these devices to repeatedly deliver the same amount of drug to a patient. The disadvantages are due, in part, to the inability to control particle size—especially when the device is used in diverse environments with greatly different humidity conditions or when differing amounts of drug are delivered into a fixed amount of air or similar quantities of drug are delivered into differing amounts of air. By adding sufficient energy to the particles to evaporate any carrier particle size is reduced to a uniform minimum and any humidity variations do not affect particle variability. Further the drug dispensing device of the present invention preferably includes electronic and mechanical components which eliminate direct user actuation of drug release. More specifically, the device preferably includes a means for measuring inspiratory flow rate and inspiratory volume and sending an electrical signal as a result of the simultaneous measurement of both (so that drug can be released at the same point each time) and also preferably includes a microprocessor which is programmed to receive, process, analyze and store the electrical signal of the means for measuring flow and upon receipt of signal values within appropriate limits sending an actuation signal to the mechanical means which causes drug to be extruded from the pores of the porous membrane.

The device 6 shown in FIG. 1 is loaded with a disposable package 1. To use the device 6 a patient (not shown) inhales air from the mouthpiece 30. The air drawn in through the opening 38 (and optionally the desiccator 41) flows through the flow path 29. The package 1 is comprised of a plurality of containers 2. Each container 2 includes a drug formulation 10 and is in fluid connection via a channel 11 with the cavity 12. The cavity 12 is covered by the porous membrane 14. A formulation heating mechanism 13 may be positioned as shown and/or an air-heating mechanism 5 located in the flow path 29. The formulation heating mechanism 13 is preferably positioned such that it is located directly below the cavity 12 when that cavity is in the drug delivery position.

The device 6 is a hand-held, portable device which is comprised of (a) a device for holding a disposable package with at least one but preferably a number of drug containers, (b) a mechanical mechanism for forcing the contents of a container (on the package) through a porous membrane (c) a heating mechanism for adding energy to formulation prior to or after it is aerosolized, and preferably further includes (d) a monitor for analyzing the inspiratory flow of a patient, (e) a switch for automatically releasing or firing the mechanical means after the inspiratory flow rate and/or volume reaches a predetermined point and (f) a source of power.

The device for holding the disposable package may be nothing more than a narrow opening created between two outwardly extending bars or may include additional components such as one or more wheels, sprockets or rollers notably mounted on the end(s) of such bars. The rollers may be spring mounted so as to provide constant pressure against the surface(s) of the package. The device may also include a transport mechanism which may include providing drive power to the roller(s) so that when they are rotated, they move the package from one container to the next. The power source 7 driving the roller(s) is programmed to rotate the rollers only enough to move the package from one container to the next. In order to use the device, the device must be "loaded," i.e. connected to a package which includes drug

dosage units having liquid, flowable formulations of pharmaceutically active drug therein. The entire device is self-contained, light weight (less than 1 kg preferably less than 0.5 kg loaded) and portable. The power source 7 is preferably in the form of standard alkaline batteries. Two 9 volt batteries could supply the heat required to heat the air which contacts the particles by about 20° C. for about 100 doses.

Energy can be added to the formulation 10 contained within a container 2 at various points. Specifically, when the formulation 10 enters the cavity 12 it can be heated by means of the formulation heating mechanism 13. Alternatively, the formulation can be forced through the pores of the membrane 14 and aerosolized and energy can be added thereafter by means of the air-heating mechanism 5 positioned anywhere within the flow path 29. The amount of energy added by the formulation heating mechanism 13 or air-heating mechanism 5 is controlled by the microprocessor 26.

Potent drugs which are highly soluble in water, ethanol and/or mixtures thereof are particularly useful with the present invention in that such drugs can be used in small amounts in high concentration and thus require less energy to obtain evaporation of the carrier. For example, a prescribed dose of Fentanyl (a highly potent narcotic) is 100 micrograms and such can be dissolved in 10 microliters of water. Particles having a diameter of 6.3 microns can be formed and subjected to evaporation to obtain a particle of one micron in diameter. In the respiratory track this one micron particle would be expected to grow to a 3 micron particle due to moisture added from the high humidity environment of the respiratory tract.

FIG. 2 is a graph which can be used in calculating the amount of energy needed to control the size of delivered droplets by controlling the amount of evaporation of carrier from the aerosolized droplets. The graph of FIG. 2 contains two types of information, the density of evaporated water vs. temperature and relative humidity, and the cooling of the air as the water evaporates. The four lines that show a rapid increase with temperature portray the density of water vapor in air, at 25, 50, 75, and 100% relative humidity. The 100% relative humidity curve represents the maximum number of milligrams of water that can be evaporated per liter of air. The diagonal lines show the temperature change of the air as the water droplets evaporate (hereafter called the air mass trajectory curves). As the evaporation proceeds, the density and temperature will change by moving parallel to these curves. To calculate these curves, air density of 1.185 grams/liter, air specific heat of 0.2401 calories/gram, and water latent heat of vaporization were assumed. These values imply that a liter of air will cool 2 celsius degrees for every milligram of water evaporated, i.e. evaporating 10 micro-liters will cool a liter of air 20 celsius degrees.

FIG. 2 can be used to calculate the amount of preheating needed to evaporate all or substantially all of the carrier in the aerosolized particles. As an example, assume the initial ambient conditions are 25° C. and 50% relative humidity. Further, assume that one wants to evaporate 10 µl (10 mgs) of water from an aqueous drug solution. Finally, assume the final relative humidity is 75%. Under these conditions the aqueous carrier would not evaporate completely. More specifically, the final particles would contain approximately equal amounts of drug and water. To calculate the amount of energy to add for this delivery manoeuvre, refer to FIG. 2. Locate the point corresponding to 25° C. and 50% relative humidity. Move up by 10 milligrams, the amount of water to be evaporated. Now move to the left until the 75% RH curve is crossed. This occurs at about 29° C. These conditions

(75% RH and 29° C.) represent the condition of the air as delivered to the patient. However, still more energy must be added to make up for the cooling of the air as the water evaporates. To calculate this amount of heat, move parallel to the air mass trajectory curves (downward and to the right) until the initial ambient water vapor density is reached, at approximately 47° C. Thus, sufficient heat to warm the air by 22C degrees must be added to achieve near complete evaporation.

FIG. 3 includes similar information with respect to ethanol which can be used in a similar manner. FIG. 2 shows the density of water vapor in air at 25°, 50° and 75° C. and 100% saturation with the air mass trajectory during evaporation also shown. The same is shown in FIG. 3 for the density of ethanol in air.

The evaporation and growth rates of aqueous droplets is a function of their initial diameter, the amount of drug dissolved therein (concentration) and the ambient relative humidity. The determining factor is whether the water vapor concentration at the surface of the droplet is higher or lower than that of the surrounding air. Because the relative humidity at the surface of a particle (i.e. droplet of aerosolized formulation) is close to 100% for all the high concentration formulations, a five micron droplet will evaporate to a 1 micron dry particle in 0% humidity in less than 20 ms. However, if a particle of drug 1 micron diameter is inhaled into the lungs (99.5% humidity) it will grow to about 3 microns in diameter in approximately one second.

The opening 38 may have a desiccator 41 positioned therein which desiccator includes a material which removes water vapor from air being drawn into the flow path 29. By reducing or more preferably eliminating water vapor from the air any water in particles of formulation can be more efficiently evaporated. Further, the particles delivered to the patient will have a smaller and more uniform size even if energy is not added to cause evaporation of water from the particles of the formulation.

The device may include a mouth piece 30 at the end of the flow path 29. The patient inhales from the mouth piece 30 which causes an inspiratory flow to be measured by flow sensor 31 within the flow path which path may be, and preferably is, in a non-linear flow-pressure relationship. This inspiratory flow causes an air flow transducer to generate a signal. This signal is conveyed to a microprocessor which is able to convert, continuously, the signal from the transducer in the inspiratory flow path to a flow rate in liters per minute. The microprocessor can further integrate this continuous air flow rate signal into a representation of cumulative inspiratory volume. At an appropriate point in the inspiratory cycle, the microprocessor can send a signal to send power from the power source 7 to the formulation heating mechanism 13 and/or air-heating mechanism 5. The microprocessor also sends a signal to an actuator which causes the mechanical means to force drug from a container on the package into the inspiratory flow path of the device and ultimately into the patient's lungs. After being released, the drug and carrier will pass through a porous membrane to aerosolize the formulation and thereafter enter the lungs of the patient.

By heating the formulation using the heating mechanism 13 any carrier in the formulation is more readily evaporated leaving behind only dry powder drug for delivery to the patient. Alternatively, or at the same time, the air-heating mechanism 5 heats the surrounding air within the flow path 29. This causes carrier in the formulation to be evaporated more readily. Thus, the only material reaching the patient is the substantially dry powder drug.

The methodology of the present invention could be carried out with a device that obtains power from a plug-in source. However, the device is preferably a self-contained, hand-held device which is battery powered. Heating mechanisms of various types can be used. For example, see the heating mechanism in the self-contained, portable sealer for plastic colostomy bags in French patent 2,673,142 which is incorporated herein by reference. A portable heater is also taught in European patent applications 0,430,566 A2 for a "Flavor delivering article" and 0,358,002 for "Smoking articles utilizing electric energy," both of which are incorporated herein by reference to disclose and describe heating components powered by batteries.

When the formulation 10 includes water as all or part of the carrier it is also desirable to include a desiccator 41 within the flow path 29. The desiccator 41 is preferably located at the initial opening 38 but maybe located elsewhere in the flow path 29 prior to a point in the flow path when the formulation is fired into the flow path in the form of aerosolized particles. By drawing air through the desiccator 41 water vapor within the air is removed in part or completely. Therefore, only dried air is drawn into the remainder of a flow path. Since the air is completely dried water carrier within the aerosolized particles will more readily evaporate. This decreases the energy needs with respect to the heating devices 5 and 13. The desiccator material can be any compound which absorbs water vapor from air. For example, it may be a compound selected from the group consisting of P₂O₅, Mg(ClO₄), KOH, H₂S₄, NaOH, CaO, CaCl₂, ZnCl₂, and CaSO₄.

It is important to note that the firing threshold of the device is preferably not based on a single criterion such as the rate of air flow through the device or a specific time after the patient begins inhalation. The firing threshold is based on an analysis of the patient's inspiratory flow profile. This means that the microprocessor controlling the device takes into consideration the instantaneous air flow rate as well as the cumulative inspiratory flow volume. Both are simultaneously considered together in order to determine the optimal point in the patient's inspiratory cycle most preferable in terms of reproducibly delivering the same amount of drug to the patient with each release of drug.

The device preferably includes a means for recording a characterization of the inspiratory flow profile for the patient which is possible by including a microprocessor in combination with a read/write memory means and a flow measurement transducer. By using such devices, it is possible to change the firing threshold at any time in response to an analysis of the patient's inspiratory flow profile, and it is also possible to record drug dosing events over time. In a particularly preferred embodiment the characterization of the inspiratory flow can be recorded onto a recording means on the disposable package.

FIG. 1 shows a cross-sectional view of a hand held, self-contained, portable, breath-actuated inhaler device 6 of the present invention. The device 6 is shown with a holder 20 having cylindrical side walls and a hand grip 21. The holder 20 is "loaded" in that it includes a package 1. The package 1 includes a plurality of containers 2.

The embodiment shown in FIG. 1 is a simple version of the invention. The device 6 may be manually actuated and loaded. More specifically, the spring 22 may be compressed by the user until it is forced down below the actuation mechanism 23. When the user pushes the actuation mechanism 23 the spring 22 is released and the mechanical means in the form of a plate 24 is forced upward against a container

2. When the container 2 is compressed its contents are forced out through the channel 11 and membrane 14 and aerosolized. Another container 2 shown to the left is unused. A top cover sheet 4 has been peeled away from the top of the membrane 14 by a peeling means 25. The embodiment of FIG. 1 could provide the same results as a conventional metered dose inhaler. However, the device of FIG. 1 would not require the use of low boiling point propellants such as low boiling point fluorocarbons. In a preferred embodiment, numerous additional features and advantages of the present invention can be obtained by utilizing the monitoring and electronic components described below.

It is important to note that a variety of devices can be used in order to carry out the methodology (including the respiratory disease treatment methodology) of the present invention. However, the device must be capable of aerosolizing drug formulation in a container and preferably does such based on pre-programmed criteria which are readable by the microprocessor 26. The details of the microprocessor 26 and the details of other drug delivery devices which include a microprocessor and pressure transducer of the type used in connection with the present invention are described and disclosed within U.S. patent application Ser. No. 07/664,758, filed on Mar. 5, 1991, now U.S. Pat. No. 5,404,871, issued Apr. 11, 1995, entitled "Delivery of Aerosol Medications for Inspiration" which application is incorporated in its entirety herein by reference, and it is specifically incorporated in order to describe and disclose the microprocessor and program technology used therewith. The use of such a microprocessor with a drug delivery device is disclosed in our earlier filed U.S. application Ser. No. 08/065,660 filed May 21, 1993 incorporated herein by reference. The pre-programmed information is contained within a nonvolatile memory which can be modified via an external device. In another embodiment, this pre-programmed information is contained within a "read only" memory which can be unplugged from the device and replaced with another memory unit containing different programming information. In yet another embodiment, microprocessor 26, containing read only memory which in turn contains the pre-programmed information, is plugged into the device. For each of these three embodiments, changing the programming of the memory device readable by microprocessor 26 will radically change the behavior of the device by causing microprocessor 26 to be programmed in a different manner. This is done to accommodate different drugs for different types of treatment.

Microprocessor 26 sends signals via electrical connection 27 to electrical actuation device 28 which actuates the means 23 which fires the mechanical plate 24 forcing drug formulation in a container 2 to be aerosolized so that an amount of aerosolized drug is delivered into the inspiratory flow path 29. A signal is also sent to the heaters 5 and/or 13 to add heat energy to the air and/or formulation. The device 28 can be a solenoid, motor, or any device for converting electrical to mechanical energy. Further, microprocessor 26 keeps a record of all drug dosing times and amounts using a read/write non-volatile memory which is in turn readable by an external device. Alternatively, the device records the information onto an electronic or magnetic strip on the package 1. The recorded information can be read later by the caregiver to determine the effectiveness of the treatment. In order to allow for ease of use, it is possible to surround the inspiratory flow path 29 with a mouth piece 30.

The electrical actuation means 28 is in electrical connection with the flow sensor 31 which is capable of measuring a flow rate of about 0 to about 800 liters per minute. It should

be noted that inhalation flow rates are less than exhalation rates, e.g. max for inhalation 200 lpm and 800 lpm for exhalation. A variety of different types of flow sensors may be used as per U.S. patent application Ser. No. 07/664,758 filed Mar. 5, 1991, now U.S. Pat. No. 5,404,871, issued Apr. 11, 1995, and U.S. patent application Ser. No. 08/002,507 filed Jan. 29, 1993, now U.S. Pat. No. 5,394,866, issued Mar. 7, 1995, which are incorporated herein by reference. The flow sensor 31 includes screens 32, 33 and 34 which are positioned approximately 1/4" apart from each other but may be comprised of a single screen or include a non-linear flow path. It is preferable to include the desiccator 41 at a point prior to the screens 32, 33 and 34 in the flow path so that the elimination of water vapor is considered in any measurement.

Tubes 35 and 36 open to the area between the screens 32, 33 and 34 with the tubes 35 and 36 being connected to a conventional differential pressure transducer 37. Another transducer designed to measure outflow through the opening 38 is also preferably included or the flow sensor 31 is designed so that the same components can measure inflow and outflow. When the user draws air through inspiratory flow path 29, air is passed through the screens 32, 33 and 34 and the air flow can be measured by the differential air pressure transducer 37. Alternatively, other means to measure pressure differential related to air flow, such as a conventional measuring device in the air way, may be used. The flow sensor 31 is in connection with the electrical actuation means 28 (via the connector 39 to the processor 26), and when a threshold value of air flow is reached (as determined by the processor 26), the electrical actuation means 28 fires the release of a mechanical means 23 releasing the plate 24 which forces the release of formulation from a container 2 so that a controlled amount of respiratory drug is delivered to the patient. The microprocessor 26 is also connected via connector 40 to an optionally present vibrating device 42 which may be activated.

Vibration device

The ultrasonic vibrations are preferably at right angles to the plane of the membrane 14 and can be obtained by the use of a piezoelectric ceramic crystal or other suitable vibration device 42. The vibrating device 42 in the form of a piezoelectric crystal may be connected to the porous membrane by means of an attenuator horn or acoustic conduction mechanism, which when correctly matched with the piezoelectric crystal frequency, efficiently transmits ultrasonic oscillations of the piezoelectric crystal to the resonance cavity and the porous polycarbonate membrane and if sized correctly permits the ultrasonic energy to be focused in a polycarbonate membrane 14 allowing for maximum use of the energy towards aerosolizing the liquid formulation 10. The size and shape of the attenuator horn is not of particular importance. It is preferred to maintain a relatively small size in that the device is hand held. The components are chosen based on the particular material used as the porous material, the particular formulation used and with consideration of the velocity of ultrasonic waves through the membrane to achieve a harmonic relationship at the frequency being used.

A high frequency signal generator drives the piezoelectric crystal. This generator is capable of producing a signal having a frequency of from about 800 kilohertz (Khz) to about 4,000 kilohertz. The power output required depends upon the amount of liquid being nebulized per unit of time and the area and porosity of the membrane (generally comprised of a polymeric plastic-like material) used for

producing the drug dosage unit and/or the efficiency of the connection.

Vibration is applied while the formulation **10** is being forced from the pores of the polycarbonate membrane **14**. The formulation can be aerosolized with only vibration i.e., without applying pressure. Alternatively, when vibration is applied in certain conditions the pressure required for forcing the liquid out can be varied depending on the liquid, the size of the pores and the shape of the pores but is generally in the range of about one to 200 psi, preferably 50 to 125 psi and may be achieved by using a piston, roller, bellows, a blast of forced compressed gas, or other suitable device. The vibration frequency used and the pressure applied can be varied depending on the viscosity of the liquid being forced out and the diameter and length of the openings or pores. In general, the present invention does not create effective aerosols if the viscosity of the liquid is greater than about 50 centipoises.

When small aerosolized particles are forced into the air, the particles encounter substantial frictional resistance. This may cause particles to slow down more quickly than desired and may result in particles colliding into each other and combining, which is undesirable with respect to maintaining the preferred particle size distribution within the aerosol. In order to aid in avoiding the particle collision problem, it is possible to include a means by which air or any other gas is forced through openings as the aerosol is forced out of the porous membrane. Accordingly, an air flow is created toward the patient and away from the nozzle opening which carries the formed particles along and aids in preventing their collision with each other. The amount of gas forced from the openings will vary depending upon the amount of aerosol being formed. However, the amount of gas is generally five to two hundred times the volume of the liquid formulation within the container. Further, the flow velocity of the gas is generally about equal to the flow velocity of the aerosolized particles being forced from the nozzle. The shape of the container opening, the shape of the membrane covering that opening, as well as the positioning and angling of the gas flow and particle flow can be designed to aid in preventing particle collision. When the two flow paths are substantially parallel, it is desirable to shape the opening and matching membrane so as to minimize the distance between any edge of the opening and the center of the opening. Accordingly, it is not desirable to form a circular opening which would maximize the distance between the outer edges of the circle and the center of the circle, whereas it is desirable to form an elongated narrow rectangle. Using such a configuration makes it possible to better utilize the air flow relative to all of the particles being forced from the container. When a circular opening is used, particles which are towards the center of the circle may not be carried along by the air being forced from the openings and will collide with each other. The elongate rectangle could be formed in a circle, thereby providing an annular opening and air could be forced outward from the outer and inner edges of the circle formed. Further details regarding such are described in U.S. patent application Ser. No. 08/247,012, filed May 20, 1994 which is incorporated herein by reference to disclose and describe such.

The device of FIG. 1 shows all of the components present within the single, hand-held, portable breath actuated device, e.g. the microprocessor **26** and flow sensor **31** used to provide the electronic breath actuated release of drug. The device of FIG. 1 includes a holding means and mechanical means and preferably operates electronically, i.e. the actuation means is preferably not directly released by the user.

The patient inhales through inspiratory flow path **29** which can form a mouth piece **30**. Air enters the device via the opening **38**. The inhaling is carried out in order to obtain a metering event using the differential pressure transducer **37**. Further, when the inspiratory flow meets a threshold of a pre-programmed criteria, the microprocessor **26** sends a signal to an actuator release electrical mechanism **28** which actuates the mechanical means **23**, thereby releasing a spring **22** and plate **24** or equivalent thereof, forcing aerosolized formulation into the channel **11**, cavity **12** (heated by the heater **13**) and out of the membrane **14** into the flow path **29** where the air surrounding the particles is heated by the air heater **5**. Further details regarding microprocessors **26** of FIG. 1 are described within co-pending U.S. patent application entitled "An Automatic Aerosol Medication Delivery System and Methods", filed on Jan. 29, 1993 as Ser. No. 08/002,507, now U.S. Pat. No. 5,394,866, issued Mar. 7, 1995, which application is incorporated herein by reference in its entirety and specifically incorporated in order to describe and disclose flow measurements, the microprocessor and program technology used therewith.

Microprocessor **26** of FIG. 1 includes an external non-volatile read/write memory subsystem, peripheral devices to support this memory system, reset circuit, a clock oscillator, a data acquisition subsystem and a visual annunciator subsystem. The discrete components are conventional parts which have input and output pins configured in a conventional manner with the connections being made in accordance with instructions provided by the device manufacturers. The microprocessor used in connection with the device of the invention is designed and programmed specifically so as to provide controlled and repeatable amounts of respiratory drug to a patient upon actuation. The microprocessor must have sufficient capacity to make calculations in real time. Adjustments can be made in the program so that when the patient's inspiratory flow profile is changed such is taken into consideration. This can be done by allowing the patient to inhale through the device as a test (monitoring event) in order to measure air flow with preferred drug delivery points determined based on the results of several inhalations by each particular patient. This process can be readily repeated when the inspiratory flow profile is changed for whatever reason. When the patient's lung function has decreased the program will automatically back down in terms of the threshold levels required for release of drug. This "back down" function insures drug delivery to a patient in need but with impaired lung function. Determination of optimal drug delivery points in the inspiratory flow can be done at each dosing event, daily, weekly, or with the replacement of a new cellular array in the device.

The microprocessor **26** of the present invention, along with its associated peripheral devices, can be programmed so as to prevent triggering the actuation mechanism **28** more than a given number of times within a given period of time. This feature makes it possible to prevent overdosing the patient. The overdose prevention feature can be particularly designed with each individual patient in mind or designed with particular groups of patients in mind. For example, the microprocessor can be programmed so as to prevent the release of more than approximately 200 μg of a given respiratory drug per day when the patient is normally dosed with approximately 100 μg of drug per day. The device can be designed to switch off this lock-out function so that drug can be delivered in an emergency situation.

The systems can also be designed so that only a given amount of a particular drug such as a respiratory drug is provided at a given dosing event. For example, the system

can be designed so that only approximately 10 μg of respiratory drug is given in a given 15-minute period over which the patient will make approximately 10 inhalations with 1 μg of drug being delivered with each inhalation. By providing this feature, greater assurances are obtained with respect to delivering the respiratory drug gradually over time and thereby providing relief from the symptoms of respiratory disease without overdosing the patient.

The microprocessor of the invention can be connected to external devices permitting external information to be transferred into the microprocessor of the invention and stored within the non-volatile read/write memory available to the microprocessor. The microprocessor of the invention can then change its drug delivery behavior based on this information transferred from external devices. All of the features of the invention are provided in a portable, programmable, battery-powered, hand-held device for patient use which has a size which compares favorably with existing metered dose inhaler devices.

The microprocessor of the present invention is programmed so as to allow for monitoring and recording data from the inspiratory flow monitor without delivering drug. This is done in order to characterize the patient's inspiratory flow profile in a given number of monitoring events, which monitoring events preferably occur prior to dosing events. After carrying out a monitoring event, the preferred point within the inspiratory cycle for drug delivery can be calculated. This calculated point is a function of measured inspiratory flow rate as well as calculated cumulative inspiratory flow volume. This information is stored and used to allow activation of the electronic actuation means when the inhalation cycle is repeated during the dosing event.

Method of Administration

The method and device of the invention provides a number of features which make it possible to achieve the controlled and repeatable dosing procedure required for the treatment of diseases, particularly respiratory diseases such as asthma. Firstly, the invention makes it possible to eliminate any carrier from the aerosolized particles and provide dry drug particles to a patient which particles can be manufactured to have a uniform size. By delivering particles of uniform size repeatability of dosing is enhanced regardless of the surrounding environment, e.g. different humidity conditions. Secondly, the device makes it possible to administer drug at the same point with respect to inspiratory flow rate and inspiratory volume at each drug delivery point thereby improving repeatability of dosing.

The method of the invention involves the release of a liquid, flowable drug from individual containers which may be interconnected in a package. This is desirable in that the liquid, flowable drug is packaged under a sterile environment and therefore does not require and preferably does not include additional materials such as antifungal, bacteriostatics, and preservatives which would normally be required in a liquid formulation if the formulation was to be opened, exposed to air, closed and later used again. The present invention does not require the use of low boiling point propellants such as low boiling point fluorocarbons. The use of such low boiling point propellants in conventional metered dose inhaler devices is desirable because such propellants eliminate the need for preservatives, antifungal and bacteriostatic compounds. However, there are potential environmental risks to using low boiling point fluorocarbons. Accordingly, the present invention provides potential

environmental benefits and would be particularly useful if government regulations prevented further use of devices which dispensed low boiling point fluorocarbons.

In addition to environmental advantages, the present invention offers advantages due to the relatively slow speed at which the aerosol dispersion is delivered to the patient. A conventional metered dose inhaler device discharges the aerosol outward at a relatively high rate of speed which causes a large amount of the aerosol particles to make contact with the inside of the patient's mouth and the back of the patient's throat. This decreases the amount of drug actually administered to the patient's lungs as compared with the present system, wherein the aerosol is delivered at a relatively slow rate of speed and can be inhaled slowly by the patient.

The method preferably uses a drug delivery device which is not directly actuated by the patient in the sense that no button is pushed nor valve released by the patient applying physical pressure. On the contrary, the device of the invention provides that the actuation mechanism which causes drug to be forced from a container is fired automatically upon receipt of a signal from a microprocessor programmed to send a signal based upon data received from a monitoring device such as an airflow rate monitoring device. A patient using the device withdraws air from a mouthpiece and the inspiratory rate, and calculated inspiratory volume of the patient is measured simultaneously one or more times in a monitoring event which determines an optimal point in an inhalation cycle for the release of a dose of any desired drug. Inspiratory flow is preferably measured and recorded in one or more monitoring events for a given patient in order to develop an inspiratory flow profile for the patient. Recorded information is preferably analyzed by the microprocessor in order to deduce a preferred point within the patient's inspiratory cycle for the release of drug with the preferred point being calculated based on the most likely point to result in a reproducible delivery event.

A flow rate monitoring device continually sends information to the microprocessor, and when the microprocessor determines that the optimal point in the respiratory cycle is reached, the microprocessor actuates a component which fires a mechanical means (and activates the vibration device) which causes drug to be forced out of the container and aerosolized. Accordingly, drug is always delivered at a pre-programmed place in the inspiratory flow profile of the particular patient which is selected specifically to maximize reproducibility of drug delivery and peripheral deposition of the drug. It is pointed out that the device of the present invention can be used to, and actually does, improve the efficiency of drug delivery. However, this is not the most important feature. A more important feature is the reproducibility of the release of a tightly controlled amount of drug (with a narrow range of particle size) at a particular point in the respiratory cycle so as to assure the delivery of a controlled and repeatable amount of drug to the lungs of each individual patient, i.e. intrapulmonary drug delivery with tightly controlled dosing. Further, this is accomplished without the use of fluorocarbons and/or bacteriostatic compounds.

The heating components and/or the desiccator to remove water vapors aid in providing repeatability in dosing in that the particles reaching the patient will have the same size regardless of the surrounding humidity. By keeping the particle size the same at each dosing event the particles deposit at the same general area of the lung at each event. These features improve repeatability along with automatic control of the drug release mechanism, combined with

frequent monitoring events in order to calculate the optimal flow rate and time for the release of respiratory drug. Further, the particles will have uniform size in that all carrier is removed regardless of the humidity of the surrounding environment. Because the drug release mechanism is fired automatically and not manually, it can be predictably and repeatedly fired at that same point in the inspiratory cycle. Because dosing events are preferably preceded by monitoring events, the point in the inspiratory cycle of the release can be readjusted based on the particular condition of the patient. For example, patients suffering from asthma have a certain degree of pulmonary insufficiency which may well change with the administration of drug. These changes will be taken into account in the monitoring event by the microprocessor which will readjust the point of release of the respiratory drug in a manner calculated to provide for the administration of an amount of respiratory drug to the patient presently needed by the patient at each dosing event.

When administering drug using the inhalation device of the present invention, the entire dosing event can involve the administration of anywhere from 10 μg to 1,000 mg of drug formulation, but more preferably involves the administration of approximately 50 μg to 10,000 μg of drug formulation. This amount of drug is in a liquid form or is dissolved or dispersed within a pharmaceutically acceptable, liquid, excipient material to provide a liquid, flowable formulation which can be readily aerosolized. The container will include the formulation having drug therein in an amount of about 10 μl to 300 μl , more preferably about 50 μl . The large variation in the amounts which might be delivered are due to different drug potencies and different delivery efficiencies for different devices.

The entire dosing event may involve several inhalations by the patient with each of the inhalations being provided with drug from the device. For example, the device can be programmed so as to release the contents of a single container or to move from one container to the next on a package of interconnected containers. Delivering smaller amounts from several containers can have advantages. Since only small amounts are delivered from each container and with each inhalation, even a complete failure to deliver drug with a given inhalation is not of great significance and will not seriously disturb the reproducibility of the dosing event. Further, since relatively small amounts are delivered with each inhalation, the patient can safely administer a few additional micrograms of drug (or milligrams for some drugs) without fear of overdosing.

In addition to drug potency and delivery efficiency, drug sensitivity must be taken into consideration. The present invention makes it possible to vary dosing over time if sensitivity changes and/or if user compliance and/or lung efficiency changes over time.

Based on the above, it will be understood that the dosing or amount of drug (and in particular respiratory drug) actually released from the device can be changed based on the most immediately prior monitoring event wherein the inspiratory flow of a patient's inhalation is measured.

Variations in doses are calculated by monitoring the effect of one or more lung function parameters in response to known amounts of respiratory drug released from each container and delivered to the patient. If the response in changing measured lung function parameters is greater than with previous readings, then the dosage (number of containers released) is decreased or the minimum dosing interval is increased. If the response in changing measured lung function parameters is less than with previous readings, then

the dosing amount is increased or the minimum dosing interval is decreased. The increases and decreases are gradual and are preferably based on averages (of 10 or more readings of lung function parameter after 10 or more dosing events) and not a single dosing event and monitoring event. The preferred drug delivery device of the present invention can record dosing events and lung function parameters over time, calculate averages and deduce preferred changes in administration of respiratory drug.

One of the important features and advantages of the present invention is that the microprocessor can be programmed to take two different criteria into consideration with respect to dosing times. Specifically, the microprocessor can be programmed so as to include a minimum time interval between doses i.e. after a given delivery another dose cannot be delivered until a given period of time has passed. Secondly, the timing of the device can be programmed so that it is not possible to exceed the administration of a set maximum amount of drug within a given time. For example, the device could be programmed to prevent dispersing more than 200 μg (or two 100 μg containers) of a particular drug within one hour. More importantly, the device can be programmed to take both criteria into consideration. Thus, the device can be programmed to include a minimum time interval between doses and a maximum amount of drug to be released within a given time period. For example, the microprocessor could be programmed to allow the release of a maximum of 200 μg of a given drug during an hour which could only be released in amounts of 25 μg with each release being separated by a minimum of five minutes.

The dosing program can be designed with some flexibility. For example, if the patient normally requires 250 μg per day of respiratory drug, the microprocessor of the inhalation device can be programmed to provide a warning after 250 μg have been administered within a given day and to continue the warning thereafter to alert the user of possible overdoses. By providing a warning and not a lockout, the device allows for the patient to administer additional respiratory drug, if needed, due to a decreased lung function and/or account for misdelivery of respiratory drug such as due to coughing or sneezing during an attempted delivery.

The ability to prevent overdosing is a characteristic of the device due to the ability of the device to monitor the amount of respiratory drug released and calculate the approximate amount of respiratory drug delivered to the patient based on monitoring a variety of lung function parameters. The ability of the present device to prevent overdosing is not merely a monitoring system which prevents further manual actuation of a button. As indicated above, the device used in connection with the present invention is not manually actuated, but is fired in response to an electrical signal received from a microprocessor (which received data from a monitoring device such as a device which monitors inspiratory flow) and allows the actuation of the device upon achieving an optimal point in a inspiratory cycle. When using the present invention, each actuation of the device will administer drug to the patient in that the device is fired in response to patient inhalation. More specifically, the preferred embodiment of the device does not allow for the release of respiratory drug merely by the manual actuation of a button to fire a burst of respiratory drug into the air or a container.

A variety of different embodiments of the dispersion device of the invention are contemplated. In accordance with one embodiment it is necessary to carry out manual cocking of the device. This means that energy is stored such as by retracting a spring so that, for example, a piston can be

positioned below the drug containing container. In a similar manner a piston connected to a spring can be withdrawn so that when it is released it will force air through the air dispersion vents. Automatic cocking of forced storing systems for both the drug formulation and the air flow may be separate or in one unit. Further, one may be manual whereas the other may be done automatically. In accordance with one embodiment the device is cocked manually but fired automatically and electronically based on monitoring the patients inspiratory flow. The formulation may be physically moved through the porous membrane in a variety of different ways. Formulation may be forced through the membrane by a piston or, without applying force to the formulation, the membrane being vibrated at frequencies sufficient to create an aerosol.

The microprocessor of the present invention preferably includes a timing device. The timing device can be electrically connected with visual display signals as well as audio alarm signals. Using the timing device, the microprocessor can be programmed so as to allow for a visual or audio signal to be sent when the patient would be normally expected to administer respiratory drug. In addition to indicating the time of administration (preferably by audio signal), the device can indicate the amount of respiratory drug which should be administered by providing a visual display. For example, the audio alarm could sound alerting the patient that respiratory drug should be administered. At the same time, the visual display could indicate "one dosage unit" as the amount of drug (number of containers) to be administered. At this point, a monitoring event could take place. After completion of the monitoring event, administration would proceed and the visual display would continually indicate the remaining amount of respiratory drug which should be administered. After the predetermined dose (indicated number of containers) had been administered, the visual display would indicate that the dosing event had ended. If the patient did not complete the dosing event by administering the stated amount of drug, the patient would be reminded of such by the initiation of another audio signal, followed by a visual display instructing the patient to continue administration.

Additional information regarding dosing with drugs can be found within Harrison's—Principles of Internal Medicine (most recent edition) and the Drug Evaluation Manual, 1993 (AMA-Division of Drugs and Toxicology), both of which are published by McGraw Hill Book Company, New York, incorporated herein by reference to disclose conventional information regarding dosing of drugs and in particular respiratory drugs as well as other useful drugs and formulations.

Supplemental Treatment Methodology

The present invention can be used to deliver many types of drugs. Specifically, the disposable packages, tapes, cassettes and drug delivery devices can be used to deliver drugs which have a systemic effect (e.g. narcotics, proteins such as insulin and antibiotics) as well as drugs which have a local effect primarily on the lungs (e.g. bronchodilators DNase or steroids). Because the present invention allows drug delivery directly to the lungs there are certain advantages with respect to using the invention for the delivery of drugs to treat respiratory diseases. For this reason, much of the operation of the invention is described in connection with the delivery of respiratory drugs. However, the invention is not limited to respiratory drugs and the examples described herein would apply with respect to the delivery of drugs

having a systemic effect. This is true also with respect to the supplemental treatment methodology described below even though this methodology is described with specific reference to respiratory diseases being treated with respiratory drugs.

Patients suffering from a given disease such as a respiratory disease may be treated solely with respiratory drug as indicated above, i.e. by intrapulmonary delivery. However, it is possible to treat such patients with a combination of intrapulmonary delivery and other means of administration such as oral administration. The oral drug is preferably given in amount so as to maintain a baseline level of drug within the circulatory system which is sufficient to maintain body functions such as lung function at an acceptable level. However, this baseline level of drug to blood ratio (or serum blood level) must be raised in order to improve the body function such as lung function during periods of stress such as respiratory difficulty such as an asthma attack and such can be accomplished by the intrapulmonary administration of a drug such as a respiratory drug using the present invention.

Based on the above, it will be understood by those skilled in the art that a plurality of different treatments and means of administration can be used to treat a single patient. For example, a patient can be simultaneously treated with respiratory drug by transdermal administration, respiratory drug via intrapulmonary administration in accordance with the present invention, and drugs which are orally administered.

The device 6 schematically shown within FIG. 1 can be specifically operated as follows. A strip 3 of containers 2 is loaded into the device 6. The device is then armed meaning that the piston such as the spring-loaded piston 24 is cocked. If applicable another piston (not shown) used to compress the liquid formulation in a dual container system is cocked. Further, a container 2 of the package is moved into position and the cover 4 is stripped off of the porous membrane 14. Thereafter, the patient withdraws air from the mouthpiece 30 and the patient's inhalation profile is developed using the microprocessor 26. After the inhalation profile is determined, the microprocessor calculates a point within the inhalation profile at which the drug should be released in order to maximize repeatability of the dosing, e.g. by plotting a curve of breath velocity versus time and determining the point on the curve most likely to provide repeatability of dosing. However, in order to carry out methodology in accordance with the present invention it is not necessary to plot any curve of breath velocity versus time. The device can be set so that the dose will be released at approximately the same point with respect to inspiratory flow rate and inspiratory volume. If the device fires at the same inspiratory flow rate and inspiratory volume each time the patient will receive substantially the same dose. Both criteria must be measured and used for firing to obtain repeatability.

Further details with respect to obtaining improved repeatability of dosing in addition to improved delivery efficiency are disclosed within a related application entitled: "Intrapulmonary Drug Delivery Within Therapeutically Relevant Inspiratory Flow/Volume Values" filed on Jul. 11, 1994, U.S. application Ser. No. 08/273,375 which application is incorporated herein by reference. The microprocessor of the present invention can be programmed to release drug (1) at the same point relative to inspiratory flow and inspiratory volume at each release of drug to obtain repeatability in dosing; and (2) to select the point within prescribed parameters of inspiratory flow rates and inspiratory volumes so as to improve the percentage amount (i.e., efficiency) of drug

delivered. In general, it is preferable to release drug when the patient's inspiratory flow rate is within the range of about 0.10 to 2.0 liters per second and when the inspiratory volume is within the range of about 0.15 to about 0.8 liters. By releasing within these two ranges it is possible to maximize the amount of drug delivered to the patient. By picking the same point with respect to both flow and volume each time it is possible to improve repeatability of dosing.

In order to produce a simple embodiment of the invention the microprocessor can be programmed within the above described ranges to release drug at the same point with respect to both inspiratory flow rate and inspiratory flow volume. This is desirable in that the microprocessor can then be programmed to allow a set amount of energy to be released to the formulation heater **13** and/or the air heater **5** which amount of energy will be sufficient to cause the evaporation of all or substantially all of the carrier within the aerosolized particles. By removing all the carrier the particle size will be smaller while maintaining uniformity thereby improving repeatability of dosing and perhaps improving the efficiency of the drug delivery system as a whole.

The drug delivery efficiency of the invention can be optimized by simultaneously or separately taking a variety of factors into consideration. For example, in addition to measuring (1) inspiratory flow rate and (2) inspiratory volume as described above one can optimize (3) particle size, (4) drug concentration in the formulation, (5) the amount of heat added, (6) the relative volume of water and/or drug to the volume of air (7) the rate of vibration (8) pore size (9) the velocity of extruded formulation (10) extrusion pressure, (11) ambient temperature and humidity, (12) ratio of water to ethanol, (13) firing point, (14) formulation viscosity, (15) solubility of drug in carrier, (16) effectiveness of desiccator, (17) shape of holes, and (18) the thickness and strength of the membrane.

After drug has been delivered it is possible to discontinue any readings with respect to flow and/or volume. However, it is preferable to continue readings with respect to both criteria after drug has been released. By continuing the readings the adequacy of this patient's particular drug delivery maneuver can be determined. All of the events are recorded by the microprocessor. The recorded information can be provided to the caregiver for analysis. For example, the caregiver can determine if the patient correctly carried out the inhalation maneuver in order to correctly delivery drug and can determine if the patient's inhalation profile is effected by the drug (e.g. with respiratory drugs) in order to determine the effectiveness of the drug in treating the patient's particular condition. If necessary, various adjustments can be made such as in the type of drug or the particle size to obtain a particular desired result.

The instant invention is shown herein in what is considered to be the most practical and preferred embodiments. It is recognized, however, that departures may be made therefrom which are within the scope of the invention and that obvious modifications will occur to one skilled in the art upon reading this disclosure.

What is claimed is:

1. A method of drug delivery, comprising:

(a) providing a disposable porous membrane having pores with a diameter in the range of about 0.25 to about 6.0 microns;

(b) forming aerosolized particles of a formulation comprised of a carrier and a drug which particles have a diameter in the range of about 0.5 to about 12.0 microns by moving the formulation through the disposable porous membrane;

(c) adding energy to the aerosolized particles by actively heating air brought into contact with the particles;

(d) inhaling the particles into the lungs of a patient; and

(e) repeating (a)–(d) wherein a new disposable membrane is provided in each step (a) and used for each forming step (b).

2. The method of claim **1**, comprising evaporating 50% or more of the carrier in the particles prior to the particles reaching the patient and wherein said adding occurs by actively heating air by moving air through a heated material which material is heated prior the patient's inhalation.

3. The method of claim **1**, comprising evaporating 80% or more of the carrier in the particles prior to the particles reaching the patient.

4. The method of claim **1**, comprising evaporating substantially all carrier.

5. The method of claim **1**, wherein the carrier is selected from the group consisting of water, ethanol and mixtures thereof.

6. The method of claim **1**, wherein the porous membrane has from 10 to 10,000 pores over an area of from about 1 mm² to about 1 cm².

7. The method of claim **1**, further comprising:

actively heating the formulation prior to moving the formulation through the porous membrane.

8. The method of claim **1**, wherein the carrier is comprised of water.

9. The method of claim **8**, further comprising:

providing a channel having a first opening into which air is inhaled, a second opening from which a patient withdraws air and a third opening through which the aerosolized particles enter the channel; and

providing a desiccator in the channel at a point after the first opening and prior to the second and third openings in a direction of flow from the first to second to the third opening.

10. The method of claim **9**, wherein the desiccator is selected from the group consisting of P₂O₅, Mg(ClO₄), KOH, H₂SO₄, NaOH, CaO, CaCl₂, ZnCl₂, and CaSO₄.

11. A method of drug delivery, comprising:

providing a volume of air;

inhaling the volume of air through a desiccator into a channel wherein the desiccator absorbs water vapor from air to obtain a volume of dried air;

providing a formulation comprised of a pharmaceutically active drug and a water carrier;

moving the formulation through pores of a porous membrane into the volume of dried air in a manner so as to form aerosolized particles and the aerosolized particles are drawn into the channel; and

continuing to inhale so as to draw the aerosolized particles and dried air into the lungs of a patient.

12. The method of claim **11**, wherein the desiccator is selected from the group consisting of P₂O₅, Mg(ClO₄), KOH, H₂SO₄, NaOH, CaO, CaCl₂, ZnCl₂, and CaSO₄.

13. The method of claim **11**, further comprising:

adding energy to the volume of dried air so as to increase the ability of the air to held a higher concentration of water vapor.

14. A method of drug delivery, comprising:

inhaling air into a channel which channel leads to an inhaling patient;

moving formulation through pores of a disposable porous membrane wherein the pores have a diameter of about 0.25 to about 6.0 microns in a manner so as to form

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aerosolized particles having a diameter in the range of from about 0.5 to about 12.0 microns wherein the formulation is comprised of a pharmaceutically active drug and a water carrier and the aerosolized particles are drawn in to the channel;

introducing water in the form of water vapor or aerosolized water particles into the air in the channel; and continuing to inhale so as to draw the aerosolized particles into the lungs of the patient;

wherein the water is substantially pure and is introduced in an amount sufficient to substantially saturate air inhaled into the channel and thereby substantially eliminate evaporation of water carrier from the aerosolized particles.

15. A method of drug delivery, comprising:

heating a formulation wherein the formulation is comprised of a pharmaceutically active drug and a water carrier;

moving the heated formulation through a nozzle in a manner so as to form aerosolized particles;

adding energy to the aerosolized articles by actively heating air surrounding the particles;

inhaling air into a channel which leads to the aerosolized particles and to an inhaling patient wherein the inhaled air is drawn through a desiccator to the channel wherein the desiccator absorbs water vapor from air; and inhaling the particles into the lungs of a patient.

16. A drug delivery device, comprising:

a channel having a first opening into which air can be inhaled, a second opening from which a patient can

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withdraw air and a third opening through which aerosolized particles enter the channel;

a container having a formulation therein;

a means for applying physical force to the formulation upon actuation;

a disposable porous membrane through which the formulation is forced through the membrane having pores with a diameter of about 0.25 to about 6.0 microns;

an air-heating device which adds energy to air inhaled into the channel; and

a means for moving disposable membranes into a drug release position for use and out of the drug release position after use.

17. The drug delivery device of claim **16**, further comprising:

a desiccator positioned in the channel at a point after the first opening and prior to the second and third in a direction of flow from the first opening to the second and third opening; wherein the desiccator absorbs water vapor from air;

wherein the device is a hand-held self-contained device having a total weight of 1 kilogram or less.

18. The drug delivery device of claim **16**, wherein the means for applying physical force to the formulation is selected from the group consisting of a piston and a vibration device.

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