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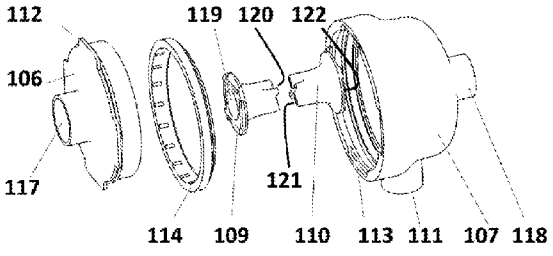

FIG 8B

(57) Abstract: An aerosol concentrator dividing an input aerosol into a respirable aerosol of an increased particle concentration and an exhaust aerosol of a lower particle concentration. The concentrator comprises a cross-slit of an input tube and output tube with a gap between the cross-slits of input tube and the output tube. A housing encompasses a plenum which encompasses the gap and is connected to an exhaust port through which an exhaust aerosol exits the plenum.

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IN-LINE PRESSURE BALANCED AEROSOL CONCENTRATOR

GOVERNMENT SUPPORT

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BACKGROUND OF THE INVENTION

Therapeutic aerosols are inhaled and deposited in the respiratory tract to treat respiratory diseases and syndromes. The impact of using many aerosol delivery devices has led to marked improvement in respiratory function and mortality, especially with those devices that deliver small molecules and micrograms of therapeutics. Many of these devices are small and readily portable. However, there is an unmet need to effectively treat those patients with severe respiratory distress due to multiple etiologies needing higher aerosol drug doses. Albeit respiratory distress impacts people of all ages, the most fragile are the young and elderly. The cost of health care on societies for these patients is also associated with high mortality.

Worldwide, there are 120 million episodes of pneumonia per year in children under 5 years, over 10% of which (14 million) progress to severe episodes resulting in 880,000 deaths/year. Most of these patients are less than 2 years of age. Also, idiopathic pulmonary fibrosis (IPF), TB, COVID-19 and chronic obstructive pulmonary disease (COPD) need deposition of the minimum effective concentrations of antivirus vaccines or anti-infectives throughout the lungs for positive outcomes. Life-saving rescue therapy for patients with hypoxemia require noninvasive treatments with pulmonary surfactant aerosols having life-saving biophysical properties.

Many potential therapeutic treatments with aerosols fail due to inadequate deposition of the active agent in the distal lungs to resolve physiological dysfunction or disease malady. This phenomenon is likely due to excessively large aerosol sizes (over 5 microns) that are deposited in the upper respiratory tract and oral pharynx as well as inadequate mass of aerosol delivery. The death of 40% of patients suffering from respiratory distress, which

includes neonates, infants, children and adults is unacceptable. Delivery of insufficient masses of agents to the lungs using inadequate aerosol devices cannot be expected to achieve a therapeutic benefit, and thus should not be used.

Atomizers generate aqueous aerosols of ~3 μm diameter at output flows of 0.3 ml/min. Compressed central axial gas flow creates a negative Venturi liquid flow to the aerosolizing nozzle where the plume is generated by Rayleigh breakup phenomena. Larger droplets are impacted on a baffle to reduce their size and are recirculated. Output aerosol flow is typically 0.3 ml/minute with 12 L/min gas flow.

Mesh type nebulizers have a vibrating mesh with typically one thousand 3 μm holes that vibrate at 128,000 cycles per second. Aerosol generation in these mesh nebulizers is severely limited by the liquid drug's viscosity. Generally, viscosities greater than 6 cP significantly reduce or prevent aerosol generation. The mesh is susceptible to clogging by liquid suspensions and large molecular drug entities. The output rates are limited to less than 1 ml/min. These devices have been incorporated with separate ventilators to provide aerosol therapy in conjunction with respiratory pressure support.

Windtree's capillary aerosol generation and delivery system incorporates Sinclair-La Mer aerosol generation. Evaporation of liquids results in aerosol nuclei. Condensation of the vapor on the nuclei results in uniform aerosols. This method can generate surfactant aerosols at 3 l/min through a delivery tube through the nose of a neonate. Losses in the aerosol generation and delivery system and tubing, combined with minute volumes of 20-40 ml/breath results in the delivery of approximately 1% of the initial volume of the surfactant liquid loaded into the system for delivery.

Trudell's Solarys nebulizer uses compressed air pressure. In this device, aerosolization occurs external to the liquid feed tip and its surrounding compressed gas ports. Generally, larger aerosol diameters and broader sprays are generated with large particle size dispersion. Also, high exit gas port pressures and aerosol velocities may injure and impact locally in the oral cavity or conducting airways of the lungs.

There is an unmet need to generate aerosols with a range of effective therapeutic moiety agents, from both low to high concentrations of drugs, over a range of low and high molecular

weights, structural molecular configurations, as well as low and high viscosities. Aerosol drugs delivered using nebulizers include broncho dilators, antibiotics, mucolytics and in future may include biologics such as pulmonary surfactant, proteins, oligomers, antibodies and nanoparticle suspensions.

Generation of fine atomized aqueous aerosols suitable for penetration through the upper respiratory airways and deposition in the peripheral lungs of neonates, infants and children with low tidal and minute volumes is challenging due to the high gas volumes and high jet velocities required, as dictated by the Weber number. Consequently, only a small volume of aerosol is usually inhaled by a pediatric patient. These physical limitations result in preference to use mesh nebulizers with their drawbacks described above as the preferred aerosol medication delivery system.

To outperform standard-of-care to treat pneumonia, higher than the minimum effective concentration of current and new anti-infectives must be delivered. Sufficient deposition of biophysical exogenous surfactant reverses inflammation induced hypoxemia in patients with pneumonia, influenza, acute respiratory distress syndrome (ARDS), asthma, COPD and cystic fibrosis.

It is therefore an object of the invention to provide an aerosol delivery system and method that overcomes the aforementioned shortcomings in the prior art. This object is achieved as by the various embodiments of this disclosure (“AeroPulsR”), which overcomes these challenges by use of its inventive liquid aerosol dispensing system to provide suitable inhalation therapeutics for treatment of a wider range of illnesses and patients.

Efficiently generating and delivering fine aqueous aerosols using pressure driven nozzles, for instance as described in the US patent 10,661,033, herewith incorporated by reference, during inspiration in children requires that small volumes of the plumes from the nozzle are either delivered directly and/or reduced in velocity using a mini aerosol concentrator as described in this specification.

To achieve the capability of partitioning the aerosol flows according to the patient’s minute volume, aerosol generation is started and stopped within few tens of milliseconds for small patients or within few seconds for adult patients. The fine particle generation by the

aforementioned nozzle utilizes pressurized liquid drug along with pressurized gas such as air, oxygen or heliox. Previously, a high-pressure syringe drive was used to deliver the liquid to the nozzle. This syringe drive was considered to be too specialized and cumbersome to be used by untrained operators, and leakage and misuse routinely resulted in liquid spillage.

Additionally, the syringe drive was unable to respond to the rapid changes of liquid flow to the nozzle necessary to meet the rapid temporal precise dosimetry requirements during inspiratory breaths in pediatric patients. This procedure requires rapid precise control of aerosol delivery during the inspiratory phase, especially for neonates and infants.

SUMMARY OF THE INVENTION

In one general aspect, the aerosol concentrator may include an input tube including: a lumen; an input tube entrance port having an input tube entrance port cross-sectional shape differing from a cross-slit shape; and an input tube exit port having a cross-slit shape, where the input tube entrance port cross-sectional shape transitions between the input tube entrance port and the input tube exit port to the cross-slit-shaped exit port cross-sectional shape. The aerosol concentrator may also include an output tube including: a lumen; an output tube entrance port having a cross-slit-shaped cross-section, said output tube entrance port being aligned with and spaced apart from the input tube exit port by a gap between the input tube exit port and the output tube entrance port; and an output tube exit port where the output tube entrance port cross-sectional shape transitions between the output tube entrance port and the output tube exit port to an output tube exit port cross-sectional shape. The concentrator may furthermore include a housing encompassing a plenum, said plenum encompassing the gap between the input tube and the output tube, where the plenum is connected to an exhaust port through which an exhaust aerosol exits the plenum.

DETAILED DESCRIPTION OF THE INVENTION

An aerosol generation and delivery system is provided for generating respirable aerosols from a liquid solution or liquid suspension. The liquid dispenser system incorporated in the aerosol generation and delivery system enables simple loading of a liquid agent into a vessel or container, and precisely meters liquid flow to the aerosolizing nozzle. The liquid to be

aerosolized may be composed of low or high molecular weight and low or high viscosity. Precise regulators adjust the compressed gas (air, oxygen or heliox) pressure with a resolution of 0.01 psi. This compressed gas is used for aerosolization of the liquid, pressurizing the liquid dispenser system and controlling the liquid flow onset or termination.

The liquid is aerosolized within an aerosolization space between an aerosol exit orifice and the liquid nozzle exit orifice. The liquid within the liquid dispenser system is maintained at a constant pressure. Maintaining a higher than liquid pressure in the aerosolization space prevents liquid from entering the aerosolization space. Conversely, reducing the pressure lower than the liquid pressure, allows liquid to enter the aerosolization space and aerosolization.

A microcontroller controlled pneumatic control system precisely synchronizes the onset and termination of the liquid flow into the aerosolization chamber with each inspiratory breath. Depending on the AeroPulsR's configuration, a low-pressure counterflowing gas is utilized to decelerate the aerosol plume from the nozzle. This counterflowing gas is delivered through a counterflow tube, exit of which is positioned axially opposite to the nozzle exit. Independent control of the counterflow gas enables optimization of aerosol concentration through dilution, as well as aerosol delivery with safe pressure for distal lung delivery.

The AeroPulsR's liquid drug flows through an axial jet into an aerosolizing space where compressed gas encompasses and shears the liquid jet. All of the liquid may be aerosolized by the nozzle and the aerosol exits the orifice as a columnar plume ensheathed within a clean gas devoid of aerosol. Depending on the nozzle configuration for a particular application, the liquid jet may exit the orifice as an aerosol plume with a fine column of aerosol particles ensheathed within a particle free gas or as a liquid jet that further disperses outside the nozzle to form an aerosol plume. This configuration results in a drip and clog free nozzle.

The liquid flow through the nozzle is dependent on the pressure difference between the liquid in the container or vial of the liquid dispenser system and the gas pressure in the aerosolizing space within the nozzle. The pressure difference between the high-pressure gas within the aerosolizing space and the aerosol exit orifice results in the shear stresses that aerosolize the liquid prior to the plume exiting the nozzle orifice. Uniform aerosols of 2 – 5 μm diameters are generated over the range of liquid flows from 0.1 ml/min to 5 ml/min, such that the mass

of aerosol generated is up to 10 times higher than that of produced by atomizers and mesh nebulizers generating similar diameter aerosols. The diameters of the aerosols are determined by the liquid flow rate, the gas pressure, its velocity within the aerosolizing space and exit orifice as well as the physicochemical properties of the liquid and its surface properties.

To generate aerosols within the ranges of 2 and 5 micron diameters, compressed gas flows (comprising of air, oxygen or heliox) within the nozzle may be generated at pressures between 40 psi and 70 psi. These pressures result in a flow of aerosol rich gas at 5 l/min and 10 l/min respectively through the nozzle (40, 50 60 and 70 psi resulted in a gas flow from nozzle of 5, 7, 9, and 10 l/min respectively). In addition, when using counterflow gas between 2 psi and 4 psi, gas flow volumes between 19 l/min and 30 l/min may be generated (counterflow tube running at 2, 2.5, 3, 3.5 and 4 psi resulted in a gas flow of 19, 22, 25, 28 and 30 l/min respectively). The rapid partitioning of specific aerosol volumes within a gas flow is dependent on the temporal activation and deactivation of the aerosol generated from the nozzle and the counterflow gas described herein. For instance, the nozzle delivering aerosol at 50 psi and counterflow gas emanating at 3 psi generate an approximate total aerosol rich gas flows of approximately 30 l/min, i.e. 500 ml/s. This total aerosol gas flow may be partitioned by rapidly activating and deactivating aerosolization and counterflow gas emanation using AeroPulsR's electronic control system. For an instance, delivering 1 liter of aerosol per breath is activated for 2 s and deactivated during exhalation. Delivering 50 ml of aerosol to an infant, aerosolization is activated for 100 ms. The volumes of the aerosol boluses and the temporal duration of these boluses may be further regulated using the pneumatic controlled system.

This rapid controlled delivery enables high concentrations of respirable tidal volumes for pediatric and adults using an identical device. The invention described here, opens the capability of delivering high doses of both new and established medication with low and high viscosity to treat respiratory tract ailments. This technology facilitates aerosol generation and gas flow synchronously with the patient's breath whether the patient is an adult, or a child with smaller lungs and higher respiratory rate. The proprietary nozzle generates fine aerosol particles of drug-containing liquids along with pressurized gases such as air, oxygen or heliox. This invention herein opens opportunities for automated delivery of aerosols boluses for respiratory aerosol delivery, as well as rapidly coating small articles with paint, glues,

powders as needed. Other applicable industrial gases include but not limited to nitrogen, argon and helium and hydrogen.

Physicians are reluctant to even temporally disconnect the patient from a ventilator to deliver an inhaled aerosol medication that would provide improved patient care. AeroPulsR integrates multiple discrete novel components that together generate and deliver aerosols with pressurized delivery gas during breaths to the lungs. AeroPulsR functions in three distinct modes as prescribed by the physician and delivers aerosol – (i) at low pressures, (ii) with modest respiratory assist or (iii) higher pressure ventilatory support. In doing so the range of medications to be aerosolized and delivered to the patient is markedly increased. Ambulatory patients who have breathing difficulty, may have the aerosol medications delivered with a suitable respiratory assist pressure using the novel bidirectional valve, as expedient. To effectively deliver high concentrations of aerosol medications to small lungs in pediatric patients, an aerosol concentrator may be included in the circuit prior to the bidirectional valve, while also providing respiratory assist as clinically required. In patients with dyspnea, a tube is connected to the aerosol output and dead-space aerosol losses are minimized. AeroPulsR with ventilation support is designed to deliver high concentrations of aerosol via the aerosol concentrator and or bi-directional valve. In bedridden patients a delivery tube connected to the console may include the concentrator attached to the bidirectional valve. At higher pressures, pulsed aerosol boluses may be delivered on demand in synchrony with the patient's breathing with breath triggering based on algorithms known in the prior art. This invention provides both therapeutic aerosol delivery and respiratory ventilatory support simultaneously to the patient.

In one embodiment, the aerosol generation and delivery system may have a main adjustable pressure regulator with an input end and an output end. The input end of the main adjustable pressure regulator may be connected to a high-pressure gas source. The main adjustable pressure regulator regulates and stabilizes the compressed gas pressure for the system and supplies compressed gas to three downstream adjustable pressure regulators. The outputs of these three downstream adjustable pressure regulators may be connected to three controllable valves to modulate the onset and termination of pressurized gas from each downstream adjustable pressure regulator.

Downstream of the main adjustable pressure regulator, the aerosol generation and delivery system may further include a first adjustable pressure regulator and a first controllable valve to ensure constant pressurization of the liquid container in the liquid dispenser system. This system supplies the liquid to the aerosol generating nozzle at a constant pressure through a delivery tube or a capillary. The aerosol generation and delivery system may further comprise a check valve provided in the liquid supply line, configured to prevent a volume flow back from the nozzle towards the liquid source. The first controllable valve is comprised of 3/2 – way valving. One inlet of the first controllable valve is open to atmospheric pressure, whereas, the second inlet is connected to compressed gas regulated by the first adjustable pressure regulator. Activation of the first controllable valve results in pressurization of the liquid dispenser system, whereas, deactivation results in venting of the pressure from the liquid dispenser system. The hardware controller of the aerosol generation and delivery system may be configured to ensure the gas pressure that equals the liquid pressure in the dispenser system essentially constant while enabling several modulating duty cycles of the pressurized aerosolizing gas in the aerosolizing space that exceeds and decreases below the liquid pressure in an alternating fashion, consequently arresting or activating aerosol generation, respectively.

The regulation of the liquid jet at the exit of the liquid nozzle, within in the aerosolization space, is provided by the main adjustable pressure regulator and a gas pressure lower than the liquid pressure supplied by a second adjustable pressure regulator. The input end of the second adjustable pressure regulator is connected to the output end of the main adjustable pressure regulator. Two input ends of the second controllable 3/2 – way valve are connected to the outlet of the main adjustable pressure regulator and the outlet second adjustable pressure regulator. The second controllable valve switches between the increased gas pressure (than liquid pressure) from the main adjustable pressure regulator and the lower gas pressure (than liquid pressure) from the second adjustable pressure regulator, resulting deactivation and activation of aerosol generation respectively.

The aerosol generation and delivery system may further include: an aerosol chamber connected with the aerosol exit orifice to receive aerosol exiting through the nozzle's aerosol exit orifice into the aerosol chamber; and a counterflow gas tube having a counterflow gas tube exit opening in the opposite direction to the nozzle's aerosol exit orifice and spaced

therefrom for decelerating the aerosol exiting through the aerosol exit orifice into the aerosol chamber.

The aerosol generation and delivery system may include a third adjustable pressure regulator provided upstream of the input of the third controllable 3/2 - way valve to modulate the onset and termination of the third gas pressure called the counterflow gas. The controller controls the third controllable valve such that the counterflow gas is switched on simultaneously with the aerosol emanating from the nozzle. The controller may also control the second and third controllable valves such that the third controllable valve supplies counterflow gas before the aerosol is generated, thus preventing aerosol deposition on the counterflow tube. This enables optimum aerosol dilution, deceleration and inside wall deposition losses.
The controller may be configured to control the second controllable valve and third controllable valve responsible for aerosol generation and counterflow gas, in conjunction with a fourth controllable 5/2 – way valve, so that aerosol generation takes place while the aerosol delivery channel port within the bidirectional valve assembly is controlled to be open; conversely the aerosol generation is stopped by controlling the second controllable valve, while the bidirectional valve assembly has closed the aerosol delivery channel port and opened an aspiration port for enabling exhalation by a patient. The common input end of the fourth controllable valve is connected to the output end of the main adjustable pressure regulator, while additional two inputs are vented to atmosphere. The fourth controllable valve switches the compressed gas between two output ends of the valve, thus opening aerosol delivery channel port or opening the expiration port within the bidirectional valve assembly. All four controllable valves' switching is controlled by the controller to maintain optimum aerosol generation characteristics.

The aerosol generation and delivery system may be configured to have the aerosol chamber comprise an aerosol chamber input end accommodating the nozzle's aerosol exit orifice of the nozzle, a counterflow tube and an aerosol chamber output end downstream of the nozzle's aerosol exit orifice and the counterflow tube, wherein said aerosol chamber output end may be connected to the recipient patient, another device or delivery tube. Alternatively, the output may be connected to an aerosol concentrator. An aerosol volume flow through the such an aerosol concentrator is designed to decrease the aerosol flow while increasing the concentration of aerosol particles at the respirable aerosol output end.

The aerosol generation and delivery system may include a bidirectional valve assembly having a bidirectional valve assembly input that connects with either the output of the chamber to a patient or device or a tube that transports the aerosol to a patient or a device. Bidirectional valve may be connected to the concentrator's respirable aerosol output end. Alternatingly opening the aerosol delivery channel port of the bidirectional valve while closing an exhalation port enables inhaling of the aerosol by a patient. Conversely, closing the aerosol delivery channel port while opening an exhalation port enables exhaling by a patient. The aerosol generation and delivery system may include a pressure relief valve connected to the aerosol chamber and/or to the bidirectional valve assembly for maintaining the desired safe pressure of the respirable aerosol to be inhaled by a patient.

An aerosol chamber output end may be included downstream of the nozzle's aerosol exit orifice and the counterflow tube, wherein said aerosol chamber output end is connected to an output cone. The output cone converges the aerosol into a laminar stream. The end of the output cone may be configured to adapt various aerosol delivery accessories, such as tubes and concentrators, through a standard medical taper cone connector.

Using the method described in this disclosure, a respirable aerosol having a fine particles size distribution of 2 – 5 μm median mass aerodynamic diameter (MMAD) may be generated. This fine particle size may be tuned such that a narrow distribution of particle size is achieved by finely adjusting the liquid flow rate. While it is expected that higher particle size distribution is possible with increased liquid flow rate, the method may be applied to a liquid solution or liquid suspension having a viscosity of up to 50 cSt, wherein conventional mesh nebulizers have a limit up to 6 cSt.

The present disclosure involves an aerosol generation and delivery system together with adjoining components to be used by a clinician for providing aerosol inhalation therapy with concurrent respiratory support. A housing may encompass several system components including electronic components, regulators, valves, a liquid dispenser system, and an aerosol nozzle chamber. The system is packaged within a robust console, which includes a user interface, a microcontroller, a hardware controller, and internal hardware. The microcontroller housed in the console is responsible for communications with the patient/clinician interface through an LCD screen which displays the treatment parameters. Treatment parameter selection and initiating commands are set by the user using a control

dial that allows inputs to the microcontroller, which controls the hardware controller. The hardware controller commands a set of controllable solenoid valves that precisely control the flow of regulated pressurized gas such as air, oxygen and/or heliox. Four precise regulators regulates and supply pressurized gases that control a variety of system functions, including: (i) stabilizing the gas pressure and limiting the maximum pressure of the system, (ii) the flow of hydraulic driven liquid from a container to a nozzle via a capillary, (iii) the liquid flow within an aerosol space, and the gas pressure and velocity for shearing the liquid to form an aerosol, and (iv) the gas pressure flow delivered by the counterflow tube. Although it is noted that four regulators are presented, addition or deletion of regulators and controllable valves may include further aerosol generation and processing capabilities. The liquid drug dispenser system is pressurized and is configured to deliver liquid to the nozzle. A counterflow regulator may be configured to regulate gas counterflow that decelerates the aerosol plume from the nozzle and provides optimum aerosol dilution with the same type of compressed gas or an economical alternative. For example, heliox is known to generate smaller particles than that of compressed air albeit expensive, may be used to generate the aerosol whereas air or oxygen compressed gas may be used for the counterflow tube. The aerosol chamber may be configured to process the aerosol and may further include a detachable cone which converges the generated aerosol downstream towards an aerosol delivery outlet. In the current invention, longer cone lengths are found to produce laminar aerosol flows near the cone delivery outlet when compared to a shorter cone length. The delivery outlet may be configured to include a desired level of respiratory support pressure. The processed aerosol comprises fine aqueous particles effective for respiratory treatment.

The electronics control and interface module (ECIM) comprises a patient/clinician interface, a microcontroller unit and a hardware controller circuit. The microcontroller, through the ECIM circuit, activates a series of fast switching controllable solenoid valves which in turn control the onset and termination sequence of the gas flows that operate the AeroPulsR system. The internal hardware may comprise four precision regulators. A main adjustable pressure regulator R regulates the input pressure P for the system. This regulator R regulates pressurized gas from a high-pressure source and maintains the gas pressure P at a constant level, typically at a preset value between 40 and 70 psi as prescribed. Although, lower or higher pressures that the aforementioned pressure range are possible. Three additional adjustable pressure regulators R1, R2 and R3 regulate gas pressure P1, P2 and P3, respectively. R1/P1 correspond to the liquid drug dispenser, R2/P2 correspond to the

aerosolizing nozzle, and R3/P3 correspond to the counterflow tube. Activation of these pressures is controlled by rapid action controllable solenoid valves. The output pressures of each of the precision regulators are preset prior to delivering the aerosol drug/agent treatment to the patient as prescribed. However, the aerosol delivery parameters, such as inhalation duration, exhalation duration and number of aerosol generation cycles for inspiration only or for continuous aerosol delivery, are set through the patient/clinician interface facilitated by the LCD screen and parameter selection dial. The gas flow is metered by the regulators and modulated by the solenoid valves to control a plurality of system components and parameters, including: the pressure of the liquid in the container, the rate of flow of the liquid to the nozzle, activating or arresting aerosol generation, the aerosol decelerating counter-flow gas flow, and the bidirectional valve that regulates the inspiration of aerosol and expiration of the breath.

The patient/clinician interface may have tactile, visual, and/or audible input and output elements for controlling the system and administering the therapy. A green push button may be included on the patient/clinician interface for providing inputs to the microcontroller that controls the timing and actuation of controllable solenoid valves. These controllable solenoid valves enable precise aerosol generation and delivery as well as the timing of the respiration and ventilation. Opening and closing of specific solenoid valves may be achieved by a microcontroller. Additionally, the patient/clinician interface may include a silver push button for switching the device ON or OFF. The patient/clinician interface may further include a simplistic layout having three LEDs and a built-in speaker, which work together to instruct the user on synchronizing their inhalation and exhalation with the device. Furthermore, for automatic aerosol delivery, a breath detection circuit in communication with the microcontroller may be used. The prescribed treatment duration for a given patient may be pre-loaded to the microcontroller in the form of software code. A therapy-specific software program may be uploaded before the treatment begins, or alternatively a pre-set therapy program may be accessed.

The pneumatic and hydraulic controls of the aerosol generation and delivery system involves a network of regulators and valves. The gas pressure of regulator R (which may be set at 50 psi), sets a maximum pressure for the entire system, followed downstream by a junction of a plurality of parallel conduits configured to direct the pressure P from the pressure regulator R into pressure regulators R1, R2 and R3, each of which provide the respective downstream

pressure control valves V1, V2 and V3. The 3/2-way control valve V1 downstream of the pressure regulator R1 controls the pressure of the liquid to be aerosolized. A 3/2-way control valve V2 downstream of the pressure regulator, R and R2 control the pressures of the gas aerosolizing the liquid and consequently the pressure in an aerosolizing space surrounding a liquid exit orifice where the liquid enters the aerosolizing space. Raising the gas pressure to P in the aerosolizing space by the pressure control valve V2 above the liquid pressure P1 results in shutting off the liquid flow through the liquid exit orifice into the aerosolizing space, which prevents liquid aerosolization. Similarly, lowering the gas pressure to P2 surrounding aerosolizing space below the liquid pressure P1 facilitates the liquid flow into the aerosolizing space. The shear of the gas pressure and velocity aerosolizes the liquid that exits through the exit aerosol orifice. For example, setting the pressure at the pressure regulator R1 to zero shuts down the liquid flow. However, during operation, a fine-tuning of the liquid pressure is necessary, which is accomplished by the pressure control valve V1.

The liquid pressure is maintained at a constant value within narrow tolerances, and the gas pressure in the aerosolizing space via the pressure controlled by the 3/2-way valve V2 that is activated within 5 ms. Thus, boluses of aerosol are depended on the pressures P and P2 which are regulated by regulators R and R2, and the delay between switching. Keeping the gas pressure in the aerosolizing space constant but modulating the liquid pressure is also possible. Also, both the liquid pressure and the aerosolizing gas pressure may be modulated simultaneously. From a practical standpoint, maintaining the liquid pressure constant within fine tolerances and adjusting the aerosolizing gas pressure within the aerosolizing space and controlling the period of V2 is the preferred solution.

To control the liquid pressure, the 3/2-way valve V1 is activated such that liquid dispenser system's container holding the liquid to be aerosolized is pressurized as required. The elevated gas pressure forces the liquid out of the container through the capillary tube, the check-valve, a liquid channel within the nozzle barrel and eventually into the liquid nozzle where it exits through the liquid nozzle output into the aerosolizing space.

A third regulated pressure P3 may be used to control a counter-flow gas via a 3/2-way valve V3, for the counter-flow that decelerates the aerosol plume that exits from the aerosolizing nozzle into an aerosol chamber. Controlling this pressure simultaneously controls the volume flow of gas exiting the counterflow tube, which in turn reduces the gas flow speed of the

aerosol plume entering the aerosol chamber. It also determines the volume of gas diluting the aerosol in the aerosol chamber.

Further, a 5/2-way controllable valve V4 is provided for controlling the aerosol flow. During inspiration, the valve V4 opens an aerosol delivery channel to allow aerosol to flow to the patient. During exhalation the valve V4 closes the aerosol flow to the patient, while simultaneously opening an expiration port to enable exhalation via a filter to outside of the system. It is also possible to synchronize the actuation of control valve V4 which is controlled synchronously with the inhaling/exhaling cycles of the patient with the pressure modulation by the valve V2 controlling the aerosol generation, and optionally along with the synchronized gas flow through the counterflow tube controlled by the pressure control valve V3 as may be needed.

The system may include a liquid dispenser system that enables the drug to be aerosolized to be easily loaded onto the AeroPulsR console. Moreover, the pneumatic liquid dispenser system is designed to enable precise control of the aerosol delivery during a patient's inspiratory cycle. The dispenser system facilitates the delivery of surfactant or other viscous or non-viscous agents using the AeroPulsR system and allows liquids of known viscosity to be precisely metered to the aerosolizing nozzle.

Compressed gas (air, oxygen or heliox) flowing through V1 is used to pressurize the dispenser system for transporting the liquid drug into the nozzle for aerosolization. A dedicated solenoid valve precisely synchronizes the hydraulic liquid flow for aerosolization with each inspiratory breath. No mechanical liquid pumps or electronic flow devices are required. In addition, handling of the liquid dispenser is configured such that this is easy for patients and clinicians to use.

The liquid dispenser system may comprise a sliding mount, a cap and drug-containing container. The sliding mount may be fixed to the AeroPulsR console. The cap may be attached to the top of the container, which may contain a liquid drug agent. For maintaining sterility of the drug, prefilled container with the cap design mentioned in this invention may be used. The container (which may for instance have a standard volume of 15 ml or 50 ml, or may alternatively be a custom volume) may be secured to the cap with a one-handed 180° twist, simultaneously achieving easy container loading and a leak proof seal. A capillary tube

for transporting the liquid drug may extend to the bottom of the container. The drug agent may be added to the container as needed without changing the capillary or the nozzle. After the container is attached to the cap, it may easily be inserted into the sliding mount affixed to the console. This insertion may be performed with one hand, in a manner similar to filling an atomizer. The sliding mount may include two ports, namely an inlet for pressurized gas and an outlet with a capillary attachment for transporting the liquid agent to the nozzle. The cap may include corresponding pressurized gas inlet and liquid outlet ports, which mate with the ports in the mount via face seals. A first face seal may be included on the container cap to seal the liquid capillary with the capillary on the cap-mount. A second face seal may be included to seal the gas pressure port. The system may also include a liquid check valve disposed between the capillary and nozzle barrel may be configured to deliver the liquid in the container to the nozzle and prevent back-flow of liquid into the container. The liquid check valve may also be situated within the liquid dispenser system. In a preferred embodiment, the total volume of the liquid inside the capillary and the nozzle barrel is less than 0.5 ml, and the entire liquid within this small volume is aerosolized at the end of the treatment.

The flow rate of the viscous liquid flowing from the container to the nozzle is dependent on four parameters: 1) Pressure difference between the container and the nozzle, 2) capillary diameter, 3) capillary length, and 4) liquid viscosity. Thus, the equation for the liquid flow rate (Q) in a capillary based on the parameters of the pressure difference (ΔP) across of the capillary, liquid viscosity (μ), inside diameter (D), and length (L), and is given by: $Q = \frac{\pi\left(\frac{D}{2}\right)^4 \Delta P}{8\mu L}$

A capillary with larger diameter may be selected for liquid agents with higher viscosities, which enables adequate accuracy and reproducibility of liquid flow generation with a pressure differential within 0.01 psi. This technique results in lower pressure losses in the system.

Precision regulator R provides the highest pressure to be used by the other regulators R1, R2, and R3. Precision regulator R is set at a constant pressure, for instance between 40 psi and 70 psi. This compressed gas output is connected to the inputs of R1, R2, and R3. A venting 3/2-way solenoid valve V1 is placed in line between R1 and the container, and passes the gas input through a cap on the container to pressurize the liquid in the container. When this 3/2-way valve V1 is off, no gas pressure is provided to the container, and the container is open to the atmospheric pressure. When valve V1 is energized, the regulated gas at

pressure P1 pressurizes the liquid container and maintains at a prescribed pressure value, typically at 50 psi. A capillary tube is included with an inlet located at the bottom of the container. The liquid from the container passes through the capillary through an inline check valve to the nozzle.

It is noted that the liquid flow is independent of the vessel volume or its liquid contents, facilitating the broader use for this liquid dispenser system. This system precisely meters the delivery of liquid solutions and suspensions of low or high molecular moieties with viscosities including, but not limited to, 1 to 60 cP. Notably, this novel pneumatic system is readily manufacturable and cost effective. The liquid container and the cap are disposable.
The aerosol generation and delivery system described herein includes a unique proprietary drip-less, clog-free nozzle that allows low and high viscosity liquids to be converted into fine aqueous aerosols. This nozzle resolves current shortcomings of other nozzles by enabling generation of aqueous viscous liquids having viscosity between 1 and 60 cP. Moreover, with the present system, liquid aerosols are generated 10 times faster (0.1 ml/min up to 5 ml/min) than with current atomizers and mesh nebulizers. The system is tuned to deliver respiratory aerosols with narrow size distributions between 2-5 μm in diameter.

The liquid in the container is maintained at a constant pressure. The liquid passes through the capillary to enter an axial channel extending through the center of the nozzle barrel. In a preferred embodiment, the liquid channel diameter is 1.2 mm and the liquid nozzle is 13.7 mm long. This axial liquid channel is radially surrounded by four gas channels. The active length of the compressed gas channel may be 20 mm, could be between 15–25 mm, or may be further lengthened or shortened depending on the nozzle's output requirements. Depending on the diameter of the nozzle barrel (9.5 mm) the number of compressed gas channels and the diameters of each channel may be optimized. In a preferred embodiment, four or more radially positioned gas channels of 1.6 mm diameter may be included within the nozzle barrel to allow for high pressure gas (air, oxygen or heliox) to be transported from the four inlet ports on the nozzle barrel. In other embodiments, gas channel diameter may be in a range between 1.2–1.8 mm, or may have a greater or lesser diameter suited to the nozzle dimensions. These input ports for the gas channels may be made at 45° angle to reduce gas flow resistance. Larger compressed gas channel diameters in conjunction with four channels used in the current embodiment, improve nozzle operation with reduced compressed

pressure gas loss. The output of the liquid nozzle and the outputs of the gas channels terminate at a small aerosolization space within the nozzle.

Aerosolization occurs within the aerosolization space when the pressurized gas and liquid converge. The aerosol exits the nozzle through an exit orifice and is expelled as an aerosol jet or a columnar plume within a sheath of gas devoid of aerosol. The resulting generated aerosol plume may form as central columnar aerosol plume that is surrounded by a sheath of gas that prevents interaction of the aerosol with the output orifice. This configuration results in a clean, drip and clog free nozzle that is resistant to exit orifice wear. A greater number of gas channels, with larger gas channel diameters, and short channel lengths, increase the gas flow rate and velocity. Collectively these conditions reduce the loss of gas pressure in the nozzle barrel and thus the aerosolization space experiences higher pressure, markedly improving the performance of the nozzle described herein, and enables the aerosol to be rapidly activated on or off.

The novel present configuration of the nozzle markedly enables rapid flow switching of the liquid on or off through periodically increasing or decreasing the gas pressure within the aerosolization space resulting in specific metered volumes of aerosol boluses for administration to adult and pediatric patients. Thus, the unique nozzle described in this embodiment enables the generation of aerosols 2-5 μm in diameter without the use of baffles to disintegrate larger droplets into respirable size aerosol diameters, as used in many atomization devices.

Using the current nozzle, a 3 ml/min flow rate of water is obtained by a slight lowering in the compressed gas pressure within the aerosolization space to 49.4 psi. The constant liquid driving pressure within the container is set at 50 psi, resulting in a negligible loss of aerosolizing pressure. The high pressure and high flow of compressed gas through the enlarged gas channels to the aerosolizing space facilitates a rapid switching of the pressure within the aerosolization space. The current nozzle generated aerosol boluses of approximately 10 ml in 30 ms, and up to many seconds of duration depending on the inspiratory requirements of the patient or the animal. The aerosolization sequence is performed until the liquid container is empty, when applicable.

The cross section of a previous, less versatile nozzle barrel and nozzle aerosolization space is shown United States Patent Publications US 8,820,662 B2; US 9573147 B2; and US 10661033 B2, and Japanese Patent Publication JP 6743280 B2, Chinese Patent Publication CN 109562237 B, and Australian Patent Publication AU 2016402362 B2, herewith incorporated by reference. In the previous prior art nozzle, a loss in compressed gas was found, requiring at least 45.7 psi to prevent control failure of liquid flow on or off.

The present invention describes a novel approach for controlling the liquid flow to be aerosolized within the aerosolization space. The liquid flow is controlled by small pressure differential pressures between the gas in the aerosolizing space and the liquid container (ΔP) and thus the aerosolization rate. The pressure in the aerosolizing space is controlled by a dedicated fast switching solenoid valve. When the gas pressure is less than the liquid pressure in the aerosolization space, the liquid is aerosolized. Conversely, when the gas pressure is higher than the liquid pressure in the aerosolizing space, the liquid flow is stopped and no aerosol is generated. More specifically, liquid flows from the liquid container to the nozzle when the pressure in the aerosolization space is less than the liquid pressure in the container. When aerosol generation should be stopped, e.g. during a time period between aerosol generation pulses, valve V2 changes P2 to higher pressurized gas P, thereby increasing the pressure inside the aerosolization space. The gas pressure of the volume between the liquid nozzle's outlet and the nozzle cap's aerosol exit orifice controls the liquid flow rate.

A one-way check valve may be attached to the capillary in the dispenser cap to prevent back-flow of liquid in the nozzle and to allow liquid flow towards the nozzle cap orifice. The pressure differential between the gas and liquid is precisely controlled within 0.01 psi, and preferably within less than 0.001 psi. When aerosol generation is desired, valve V2 facilitates an interchange of pressure between P2 and P, as discussed. When the gas pressure in the aerosolization space is reduced below the liquid pressure, liquid flows into the aerosolization space and fine aerosols are generated. Precise control of gas flows and liquid flows through the nozzle can be typically controlled between 0.1 ml/min and 5 ml/min. Although higher flow rates of up to 20 ml/min were achieved with subsequently larger aerosol particle sizes being observed. This control of flow rate is achieved by reducing the pressure within the aerosol space according to the viscosity of the liquid, with differential pressures constraints between 0 and 2 psi for low viscosity liquids and could increase based on viscosity of the liquid used.

Higher differential pressure results in higher liquid flow rate and subsequently larger aerosol particle sizes. High viscosity liquids require a higher pressure differential and/or a larger internal diameter capillary.

The gas pressure interacts with the liquid from the liquid nozzle to aerosolize the liquid into a fine plume. When the gas pressure regulated by regulator R2 is lower than the liquid pressure, the flow is proportional to the pressure differential between the liquid and the gas. When the gas pressure regulated by system regulator R is larger than 0.5 psi, the liquid flow is prevented and the aerosol generation stops. This sequence is repeatable as needed. The pressure in the container is vented to the atmosphere via the vent port on valve V1 after aerosolization is finished, to prevent the pressure in the container from increasing. This stops further liquid entering the nozzle and prevents dripping from the nozzle.

The velocity of the aerosol plume generated by the nozzle is reduced as the aerosol passes through a chamber. The chamber contains the axial counterflow tube through which a precisely regulated gas flow opposes the velocity of the aerosol emanating from the nozzle. The control of this counter-flow gas finely enables the deceleration of the nozzle exit plume, as well as stops gas flow during expiration, thereby minimizing the use of heliox or other compressed gas used for aerosolization. This virtual baffling phenomenon reduces the aerosol velocity and results in a uniformly distributed aerosol plume within the chamber. The total aerosol output is dependent on the total gas flow through the aerosolizing nozzle and the counter flow tube. Depending on the configuration, wall deposition of the aerosol within the aerosol chamber and cone sidewalls limits the output of the aerosol generation and delivery system to 30%. Absence of a counterflow gas results in higher aerosol losses due to high velocity deposition on the sidewalls of the converging cone. The counterflow tube has an independent gas source, and receives gas at pressure P3 regulated by regulator R3. The gas flow from the counterflow tube is switched on or off independently using a dedicated fast switching solenoid valve. Typically, the onset of the counterflow gas is activated prior to activating the aerosol generation through the nozzle and deactivated following generation of aerosol from the nozzle.

A 3/2-way solenoid valve V3 switches the gas flow on or off 50 ms before and after the aerosol is switched on or off, respectively. This procedure is performed to conserve the amount of gas, such as heliox, required for aerosolization and control the total output flow rate from the

system. In an alternate embodiment of the invention, the counterflow tube control and gas supply may be made inter-dependent by having a common compressed gas inlet port for both the nozzle and the counterflow tube. This configuration further simplifies the pneumatic liquid aerosol system by eliminating R3 and V3.

The slowed aerosol generated within the chamber may be delivered using a delivery cone. This cone may be fitted to the chamber using a lip seal or other sealing mechanism that mates with the chamber exterior wall of the chamber. The length of the cone and internal shape are optimized to minimize wall deposition of the aerosol and to provide a soft aerosol exiting the output cone. The cone output port is designed to connect with other AeroPulsR related complementary aerosol delivery devices, such as the aerosol concentrator and bidirectional valve assembly. In certain embodiments, the cone may have a length of 70 mm, 100 mm, or 150 mm, and the specific delivery cone dimensions will depend on the application of the device, for instance the size of the patient, especially since the aerosol generation may be partitioned for suitable delivery for patients ranging from infants to adults. Generally, longer cone lengths correspond to a longer length of laminar flow region near the cone output, which may be advantageous for facilitating smoother aerosol delivery to a patient.

The combination of the aerosol chamber and delivery cone forms the shape of a pod, which rests on a pedestal. Aerosol that is deposited on the sidewalls of the chamber and cone may drain through a drain hole into a condensation collection well built into a pedestal. The combination of the chamber and delivery cone is able to house the aerosolizing nozzle, counterflow tube and the aerosol before delivery in a compact manner with minimum losses of aerosol. The chamber may include two ribs that match with two matching notches on the pedestal to allow for easy installation and removal. This configuration allows the user to disassemble the elements within the chamber and cone for cleaning and maintenance.

In another embodiment, the AeroPulsR system may be configured to deliver aerosols on-demand, for which several of the system's capabilities are not required. In this embodiment, the container may be charged with a prescribed dose volume and mounted onto the console. Similar to generic atomizers, the system may include a wye piece comprising a mouthpiece and exhalation port along with an exhaust filter. The aerosol generation may for instance be set at a dose rate between 0.1 and 5 ml/minute, i.e. up to 10 times greater than alternative aerosol generation delivery devices. A dose rate of 0.3 ml/min is typical for atomizers used to

output aerosol diameters of 3 μm median mass aerodynamic diameter (MMAD), whereas the AeroPulsR system allows up to at least 3 ml/min to be inhaled through the mouthpiece. Upon activating the AeroPulsR system, the patient breathes until the dose of the liquid in the container is depleted. This may allow the drug delivery time to be markedly reduced to a fraction of the delivery time of a generic atomizer. In certain embodiments, the drug delivery time may be reduced to 1/10th of the delivery time of a generic atomizer.

In a preferred embodiment, the AeroPulsR system may be configured to deliver aerosol with a pressure assist. This capability enables expansion of the patient's lung and airways volumes to improve aerosol drug penetration and deposition. In one embodiment, a bidirectional valve may be attached directly to a cone. In another embodiment, the bidirectional valve may be connected to the cone via a wye, wherein the wye may include a filter and a pressure release valve. The bidirectional valve assembly comprises an aerosol inlet, an aerosol outlet, and an expiration port. During inhalation, the bidirectional valve allows the aerosol to enter through the inlet and pass through an aerosol delivery channel port to the patient, while the bidirectional valve concurrently occludes the expiration port. The patient's inspiratory volume is governed by the gas pressure of the aerosol in the chamber and cone. During exhalation, the bidirectional valve opens the expiration port, while occluding the aerosol delivery channel port. The opening of the expiration port enables the patient to exhale through a very low resistance. Simultaneously, to vent the pressure generated inside the chamber-cone, the excess pressure is vented through a pressure relief valve, which may be set or adjustable. In a preferred embodiment, the bidirectional valve assembly comprises a flap valve operated pneumatically through a 5/2-way solenoid valve V4 in the console.

In one embodiment of the invention, a wye-piece may be attached to the aerosol delivery cone. The patient inhales aerosol when required. The excess pressure generated within the aerosol chamber and wye piece releases through a pressure relief valve attached to the wye.

In one embodiment of the invention, a delivery tube attached to the medical taper end of the cone enables positioning of the bi-directional valve and inline concentrator next to the patient's mouth, enabling high concentration aerosol delivery. The inline concentrator may be removed when required, resulting an alternate arrangement of the aforementioned embodiment.

Notably, there are no electrically conducting wires near the patient. Using pressure P regulated by the primary regulator R, the 5/2-way valve V4 may switch the direction of pressure, resulting in a 90 degree angular motion of the bidirectional valve. When the aerosol is generated for inspiration, a corresponding control signal is transmitted to the 5/2-way valve V4 to switch the pressure. This procedure results in a 90° rotation of the bidirectional flap valve, thereby opening the aerosol delivery channel port so that aerosol may be delivered to the patient. The rotation of the bidirectional flap valve simultaneously closes the expiration port. When the 5/2-way valve V4 switches the pressure to an alternate position, the bidirectional flap valve closes the aerosol passage, while simultaneously opening the exhaust port, thereby facilitating exhalation by the patient.

In one embodiment, the nozzle may include a 500 µm diameter exit orifice and a gas flowrate of 30 L/min. Aerosol may be generated and delivered either continuously or in defined boluses during inspiration. This functionality is achieved by the synchronous activation and deactivation of aerosol generation dictated by the nozzle and the bidirectional valve. As discussed, aerosol may be generated or arrested in the nozzle by controlling the pressure in the aerosolization space within the nozzle. The aerosol velocity may be reduced in the chamber and cone by a counterflow tube. Subsequently, the bidirectional valve may delay the aerosol's delivery times, as necessary. To deliver aerosol pulses between 50 ml and 2 L, the liquid aerosol generation pulse duration may be selectable between 100 ms and 4 s, respectively. The final aerosol inspiratory and expiratory breaths by the patient are synchronized by the bidirectional valve, when prescribed.

Tidal volume for inspiration and periodic breath rate are determined according to the size of the patient. To increase the drug concentration while retaining the tidal volume, an aerosol concentrator may be placed in between the cone and the bidirectional valve. The cone, concentrator and bidirectional valves maybe configured to be easily interconnected or disconnected, but with sufficiently secure connections to prevent leakages. The volume of the aerosol is dependent on the volume of the aerosol chamber as well as additional gas from the counterflow tube. These parameters control the dilution of the overall aerosol concentration. An aerosol concentrator may be incorporated to reduce the volume of the gas. The concentrator may comprise accelerating/converging slits and decelerating/diverging slits separated by 1.5 mm gap.

The concentrator comprises four parts. The upstream side of the concentrator comprises an upstream plenum and an upstream accelerating nozzle, whereas the downstream side comprises a downstream plenum and a downstream decelerating nozzle. The nozzles comprises lobes whereas the plenum includes matching indentations. When attached rigidly, the nozzles align such that a gap between 1.5 to 2.5 mm is ensured between the exit of the accelerating nozzle and entrance of the decelerating nozzle. The shape of the exit and entrance of the accelerating and decelerating nozzle, respectively, are formed of linear cross slit, and hence the embodiment is also referred as the cross-concentrator. Four lobes in the upstream plenum mate with four indentations in the downstream plenum. The lobes and indentation on the nozzles' base and plenums' interior, as well as the lobes and indentation on the plenums ensure that the cross slits of the accelerating and decelerating nozzles align accurately. The upstream plenum aligns with the downstream plenum and attaches through a lip-seal, which ensures leak proof operation. The width of these slits are 1 mm in the exit of the accelerating nozzle, whereas, 1.5 mm in the entrance of the decelerating nozzle. The inlet of the concentrator is readily attached to the aerosol output cone and the output port of the concentrator adapts with the bidirectional valve, a wye, or an aerosol delivery tubing.

When aerosol at approximately 30 l/min flows through the input of the accelerating nozzle, the high inertia aerosol particles of 2 µn and higher enters the decelerating nozzle, whereas, low inertia particles and particle free gas are lost through the gap. This exhaust gas is routed through an exhaust port on the downstream plenum. This phenomenon results in decrease of gas flow rate through the concentrator to up to 1/5th of the initial volume flow of the gas, where 4/5th of the gas volume is exhausted. The majority of the aerosol is dispersed in the 1/5th of the flow through the concentrator and is delivered to the patient.

Due to their momentum, the higher inertial aerosol particles (2-5 µm in size) pass though the slits and through the gap into the decelerating slits, whereas lighter particles and dilution gas (<1 µm in size) escape through the sides of the gap and exit through the exhaust port in the concentrator. By having the dilution gas and other non-aerosol particles escape through the exhaust port, a high concentration of aerosols is outputted. The concentrator maintains the mass of the aerosolized drug, resulting in up to a fivefold increase in the aerosol concentration.

Generation of fine respirable particle aerosols through a nozzle requires a high gas velocity to shear the liquid into fine particles and a high gas mass. This combination results in a continuous generation of large aerosol volumes necessary for the respiratory needs of adults, infants and children, as well as animals. The aerosol generation and delivery system described herein, AeroPulsR, generates aerosol volumes of 10 ml in 30 ms to several liters in several seconds (2 L in 4s) depending upon the patient's tidal and minute volumes. The aerosol flows may be reduced with simultaneous increase in drug concentration using suitable aerosol concentrators, such that aerosol tidal volumes are delivered to pediatric and adult patients. The impact of the AeroPulsR's introduction is expected to have wide applicability for multiple inhalation therapeutics to more effectively treat a range of respiratory diseases.

Although this invention is primarily described for the delivery of therapeutic aerosols to the lungs in patients with respiratory ailments, technologies comprising AeroPulsR can be readily applied and expanded towards animal research and healthcare to treat mammals such as horses, companion animals, livestock and fowls. In addition, these technologies are suitable for automation of spraying paints, glues, disinfections and other suitable agents.
The present invention contemplates and solves a variety of objective technical problems through the specific structural features and method steps disclosed in this description.

A first objective is enabling aerosolization of both low to high molecular weight aqueous solutions of low and high viscosities. This object is achieved by utilizing a single-pass nozzle, which may be configured to generate required respiratory aqueous aerosols (2-5 μm diameter, Dv50) and deliver these either continuously or only selectively during inhalation to conserve the API agent.

A second objective is to delivers inspiratory tidal volumes at relevant inspiratory rates for neonates, infants, children and adults (and animals), as appropriate. This object is achieved by using a pneumatic driven electronic control system to precisely regulate medicament delivery volumes and rates according to demands.

A third objective is to deliver low as well as very high masses of aerosols during inspiration of respiratory aerosols as appropriate for all ages. This object is achieved by adjusting the

liquid drug flow rate between 0.1 ml/min and 5 ml/min, and when appropriate up to 20 ml/min, thereby providing versatility and adaptability tailored to different applications.

A fourth objective is to generate an aerosol from a liquid in an aerosolizing space within the single-pass nozzle. This object is achieved by providing advantageous dimensions, spacing, and structural arrangement. This space is located between a liquid jet exit ~250 μm in diameter, and the entrance of the nozzle's aerosol exit orifice. The distance between the pressurized liquid jet exit and the aerosol exit orifice is typically 2 mm. The aerosol exit orifice diameter between 300 μm and 1,200 μm is utilized such that the aerosol plume is generated within this aerosolization space. This arrangement results in the aqueous aerosol plume exiting such that it is ensheathed by aerosol free gas, enabling negligible contact of aerosol with the internal surfaces of the nozzle and aerosolization space and drip-free nozzle. This phenomenon also results in a nozzle that is free of particle and liquid deposition on the aerosolizing nozzle surfaces, prolonging nozzle operation without clogging.

A fifth objective is to precisely control the gas pressure within the aerosolization space such that the aerosol generation is precisely metered. This object is achieved by providing gas pressure either higher or lower than the liquid jet pressure at the exit of the liquid nozzle orifice. Advantageously, the liquid flow of the liquid jet, and consequently the aerosol generation, is controlled between zero and a liquid flow rate within the range of 0.1ml/minutes to 5 ml/ minute, but may be as high as 20 ml/minute.

A sixth objective is to minimize the resistance of the flow of the compressed gas through the single-pass nozzle. This objective is achieved by having gas flow into at least four inlet channels that connect at an angle of 45 ° to at least four compressed gas channels along the nozzle's barrel. In a preferred embodiment, these channels are 1.6 mm in diameter and 20 mm long, and via an annular buffer, enable the gas to enter into a small pressure space equalizing into the aerosolizing space. This configuration enables precise flow control of the input liquid jet with a minor compressed gas pressure differential of less than 0.5 psi within the aerosolizing space. Precise pressure regulators enable fine pressure differential adjustment. Controlled rapid acting valves enabled liquid flow control with the compressed gas and with minimal pressure differentials of typically 0.5 psi, that are activated in less than 5 ms. In another demonstration, consistent aerosol boluses were obtained with pulse

durations of 250 ms and up to several seconds. These are programmed on the control dial of the console and are selected by the operator. Accordingly, the reduced resistance achieves several advantageous effects, including more rapid switching speed and more consistent aerosol boluses.

A seventh objective is to precisely synchronize the liquid aerosolization with the patient's breathing, together with that of a gas counter-flow, when prescribed. This object is achieved by pressure modulation by valves respectively controlling aerosol generation and gas flow through a counterflow tube, which may be actuated in synchrony with breathing.

An eighth objective is to prevent the liquid against exposure to metal or other non-biocompatible surfaces. This object may be achieved through the elimination of any mechanical pinch valve or other mechanical metal device in contact with the liquid within the nozzle or elsewhere.

A ninth objective is to achieve rapid response times, eliminate cleaning related issues, as well as contribute to minimizing the dead-space of the liquid between the liquid vessel/container and the single-pass nozzle. This object is achieved by the elimination of any mechanical liquid pump, including syringe drives.

A tenth objective is to precisely maintain a constant pressure within the liquid dispensing system independent of the vessel volume or the gas or liquid within the vessel. This object is achieved through precise metering and advantageous valve configuration.

An eleventh objective is to rapidly activate or deactivate aerosol generation. This object is achieved through a collection of advantageous gas channel conditions, including a greater number of gas channels, larger gas channel diameters, and short channel lengths.

A twelfth objective is to transport the liquid containing drug from the liquid in the vessel to the liquid input of the nozzle. This object is achieved using a precision capillary such that the liquid channel transports the liquid to the aerosolizing space within the nozzle.

A thirteenth objective is to enable the initiation of the aerosol generation for the initial and last breath of the patient as well as each and every breath in between. This object is achieved by

precisely controlling the hydraulic liquid pressure to meter the liquid flow rate, thus aerosol generation, and pneumatic gas pressure to regulate the aerosolization rate through the exit orifice.

A fourteenth objective is to enable aerosol delivery during inhalation and exhalation of the breathing cycle, and thus optimize aerosol delivery to the patient. This objective is achieved at least in part by controlling the operation of a low resistance pneumatic bidirectional valve.

A fifteenth objective is to minimize hazards to patient during use of the device. This object may be omitting any electrical wires that may come in contact with the patients, or safely housing wires to avoid contact.

A sixteenth objective is to eliminate any electrocution risks and enhance the portability of the device. This object is achieved by powering the valves and control system with low voltage and currents using a battery.

A seventeenth objective is to rapidly and precisely partition the constant aerosol generation rate from the nozzle into specific tidal volumes to be inhaled into the lungs of a neonate, infant, child, adult, or an animal, at a required respiratory rate. This object is achieved through temporal activation and deactivation of aerosolization and counterflow gas emanation using a control system.

An eighteenth objective is to facilitate the automation of processes including spraying of agents such a paints, glues or other liquid that requires automation for industrial, commercial and other trades. This object may be achieved through the incorporation of a breath detection circuit, which may for instance be in communication with a microcontroller.

A nineteenth objective is to optimally process output aerosol based on application requirements. This object may be achieved using AeroPulsR's accessories, such as in-line concentrator, bi-directional valve and delivery cone with different lengths, which produce varying advantageous output effects suited for different purposes.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a block diagram of the components of the aerosol generation device.

FIG. 2 is a schematic diagram of the pneumatic system and aerosol generation device.

FIG. 3 shows an exploded view of the liquid dispenser system.

FIG. 4A shows the assembled perspective view of the dispenser system.

FIG. 4B shows an alternate exploded view of the dispenser system as shown in FIG. 3

FIG. 5A shows the side view of the dispenser cap.

FIG. 5B shows the longitudinal section denoted A-A in FIG. 5A.

FIG. 5C shows the top view of the dispenser cap.

FIG. 5D shows the vertical section denoted B-B in FIG. 5C.

FIG. 6A shows a perspective view of the nozzle.

FIG. 6B shows the side view of the nozzle and the sectional view denoted D-D.

FIG. 6C shows the sectional view denoted C-C in FIG. 6B.

FIG. 6D shows a detailed view denoted as Detail A in FIG. 6C.

FIG. 7A shows a perspective view of an assembly comprising a nozzle, aerosol chamber, counter flow tube, chamber pedestal, aerosol concentrator and flapper block.

FIG. 7B shows the top view of assembly in FIG. 7A.

FIG. 7C shows the sectional view denoted D-D in FIG. 7B.

FIG. 8A shows an assembled perspective view of the aerosol concentrator.

FIG. 8B shows an exploded view of the aerosol concentrator.

FIG. 8C shows the assembled side view of the aerosol concentrator.

FIG. 8D shows the sectional view denoted E-E in FIG. 8C.

FIG. 9A shows a perspective view of the flapper block.

FIG. 9B shows an exploded view of the flapper block.

FIG. 9C shows the top view of the flapper block.

FIG. 9D shows the sectional view denoted F-F in FIG. 9C.

FIG. 10 shows a plot of particle size versus flow rate for PVP solutions of different viscosities aerosolized using compressed air and a 500 μm orifice nozzle.

FIG. 11 shows a plot of particle size versus flow rate for PVP solutions of different viscosities aerosolized using compressed heliox and a 500 μm orifice nozzle.

FIG. 12 shows a plot of particle size versus flow rate for PVP solutions of different viscosities aerosolized at a lowered pressure using compressed air and a 500 μm orifice nozzle.

FIG. 13 shows a plot of particle size versus flow rate for PVP solutions with different viscosities are aerosolized using compressed air and a 700 μm orifice nozzle.

FIG. 14 shows a three-axis plot particle size versus flow rate and particle size versus span, when with a 500 μm orifice nozzle water is (i) aerosolized using compressed air, and (ii) aerosolized using heliox.

FIG. 15A shows a plot of the aerosol bolus intensity versus time using the nozzle according to one embodiment of the invention with the system.

FIG. 15B shows a magnified view of a plot of the intensity of a single bolus versus time using the nozzle according to one embodiment of the invention with the system.

FIG. 15C shows a plot of the aerosol bolus intensity versus time using a prior art nozzle.

FIG. 15D shows a magnified view of a plot of the intensity of a single bolus versus time using a prior art nozzle.

DETAILED DESCRIPTION OF THE DRAWINGS

FIG. 1 is a block diagram schematically demonstrating the components of the aerosol generation device. The invention comprises a console 1 and its components which interact with the patient/clinician via a patient/clinician interface 2 to deliver precise doses of aqueous aerosols as shown in FIG. 1. The console 1 may comprise the patient/clinician interface 2, microcontroller 3, hardware controller 4 and internal hardware 5. Several components, including the liquid dispenser 6, aerosol nozzle 7, counterflow tube 8 and the aerosol delivery respiratory support 9, are pneumatically controlled by the hardware controller 4 which comprises solenoid valves that are triggered by the microcontroller 3. The patient/clinician interface 2, microcontroller 3 and the hardware controller 4 forms the electronic control and interface module (ECIM) 147. The settings for the microcontroller 3 and internal hardware 5 may be set in accordance with a prescribed dosage. When the patient/clinician initiates the therapy via the patient/clinician interface 2, the microcontroller 3 interacts with the hardware controller 4 to effect aerosol output. The aerosol chamber 10 comprises the aerosol nozzle 7 and the counterflow tube 8, both of which are housed therein. The aerosol chamber 10 is configured to focus the aerosol generated by the nozzle 7 downstream. The aerosol delivery respiratory support 9 enables delivery of the aerosol to the patient, and ensures aerosol is only delivered during inhalation.

FIG. 2 schematically shows the system according to the invention. Compressed air or heliox is supplied to the system by a high-pressure source 20, and regulated by a main system pressure regulator 21, which is connected in series with the high-pressure source

20. This stable and regulated pressure is then distributed downstream to the constituent systems through a gas supply line network.

Pressure may be routed to a liquid container 23 through a gas supply line 13, along which a liquid pressure regulator 22 and a 3-2-way solenoid valve 24 are disposed. The liquid pressure regulator 22 may be configured to pressurize the liquid container 23, which supplies liquid to the aerosol nozzle 7 via a liquid supply line 11. A 3/2-way solenoid valve V1 24 may be disposed between the liquid pressure regulator 22 and the liquid container 23 to control the flow of liquid from the liquid container 23 to the nozzle liquid input 60 of the nozzle 7. In a preferred embodiment, the 3/2-way solenoid valve 24 is by default in a vented position, and prior to aerosolization may switch to an open position, thereby allowing the inlet of the compressed gas pressure from R1 pressure regulator 22.

The system may additionally include a 3/2-way solenoid valve 26 configured to control the flow of liquid within the liquid channel 70 inside the nozzle barrel 66. Regulated pressures from the main system pressure regulator 21 and a nozzle gas regulator 25 are routed through the 3/2-way solenoid valve 26. The pressures P, P1 and P2 respectively corresponding to the system regulator R 21, liquid pressure regulator R1 22 and nozzle gas regulator R2 25, are adjusted such that P > P1 > P2. When the V2 26 is open to pressure P from regulator R 21, the pressurized liquid flow in the aerosol nozzle 7 is arrested. However, when the V2 26 is open to pressure P2 from regulator R2 25, the liquid flows through the aerosol nozzle 7 for aerosolization. The 3/2-way solenoid valve 26 is capable to alternatingly between P and P2 within 5 ms duration.

Pressure may be routed to counterflow tube 8 via a counterflow gas tube supply line 14 and expelled out of a counterflow gas tube exit opening 16. A counterflow tube regulator 27 may be included to control the gas pressure in the counterflow tube 8. A second 3/2-way solenoid valve 28 may be included intermediate to the counterflow tube regulator R3 27 and counterflow tube 8. When in its default closed position, the 3/2-way solenoid valve 28 allows for independent control of the counterflow tube 8. The electronic control and interface module (ECIM) 147 may be configured to control the respective valves.

A 5/2-way solenoid valve V4 29 may be included to control the pressure output to the aerosol delivery respiratory support 9, which comprises a bidirectional valve assembly 130.

Two pneumatic lines 31 extend between the 5/2-way solenoid valve 29 and a pneumatic actuator 43 located at the bidirectional valve assembly 130. Pressure regulated by the system pressure regulator 21 may be switched between the two pneumatic lines 31 in order to open and close the aerosol delivery channel port 136 of the bidirectional valve assembly 130, thereby controlling whether the aerosol output to the patient is allowed or arrested.

Figures 3–5 show various views of the liquid dispenser 6, which supplies liquid drug to the nozzle 7. A liquid container 23 is screwed into the dispenser cap 41, and then is slid into the dispenser mount 42. In a preferred embodiment, the liquid container 23 may contain standard liquid volumes such as 15 mL or 50 mL, but the volume of the container 23 may be any volume suitable for a given dosage or usage. The container 23 may include half turn threads 45 configured to mate with cut threads 44 on the dispenser cap 41. This configuration promotes easy loading by achieving coupling with only a half twist of the container 23.

The dispenser mount 42 may include a front recess through which the dispenser cap 41 is inserted, a back wall opposite the front recess, a top surface, and two side walls. The back wall of the dispenser mount 42 may include two threaded holes 46 for mounting the dispenser assembly onto the console 1. The liquid container 23 is pressurized through a threaded port 47 located between the two threaded holes 46 on the back wall of the dispenser mount 42. The threaded port 47 extends to a perpendicular hollow channel 48 inside the dispenser mount 42 that directs the compressed gas downwards into the container 23 (FIG. 5B). As shown in FIG. 5B and FIG. 5D, a through channel 56 is included on the top surface of the dispenser mount 42. The through channel 56 includes threads for connecting the nozzle 7 to the dispenser mount 42 via a male luer lock fitting and a capillary. The dispenser cap 41 may include a locking mechanism comprising two cantilever clips 50 with slots 51 configured to interface with corresponding keys 52 located on sliding tracks 53 in the interior side walls of the dispenser mount 42. Each of the cantilevers 50 may include a ramped section such that the cantilevers 50 must be pinched to fit onto the sliding tracks 53 when inserting the dispenser cap 41 into the dispenser mount 42. When the dispenser cap 41 is fully inserted into the dispenser mount 42, the keys 52 on the dispenser mount 42 fall into the slots 51 of cantilevers 50, thereby creating a secure connection between the dispenser cap 41 and dispenser mount 42. Two O-rings 57 may be included in the liquid delivery port 58 to create an air and fluid tight seal when the dispenser

cap 41 is slid into the dispenser mount 42. Additionally, the sliding tracks 53 on the dispenser mount 42 may be configured such that the O-rings 57 are compressed when the dispenser cap 41 is inserted into the dispenser mount 42. A capillary section and an inline check valve may be threaded to the liquid delivery port 58 on the dispenser cap 41.

FIG. 6A shows the external structural components of the nozzle 7, which may include a knob 65, barrel 66, nozzle cap 68, and male luer connector 148. Nozzle 7 includes a nozzle liquid input 60, a nozzle gas input, and an aerosol exit orifice 15. The liquid is fed from the liquid container 23 to the nozzle liquid input 60 via a liquid supply line 11, which may for instance be a capillary. In a preferred embodiment, the knob 65 may include threads 69 to allow a capillary to be connected to the nozzle 7 via a male luer connector 148. The liquid may then be fed through a liquid channel 70 running axially through the lengthwise axis of the nozzle barrel 66 between the nozzle liquid input 60 and the fluid exit 75, as shown in section view C-C FIG. 6C. Gas flows to the nozzle gas input via a gas supply line 12, and is fed to a plurality of air channels 71, which may be aligned adjacent to the liquid channel 70. Preferably, as shown in FIG. 6B, the air channel diameter 141 is maximized for minimum air resistance, and the liquid channel diameter 142 may be optimized to reduce liquid flow resistance. In a preferred embodiment, four air channels 71 are included inside the nozzle 7. Each air channel 71 may have a corresponding hole 72 in the nozzle barrel 66 through which the gas may flow in. For reduced flow resistance to the gas, the gas inlet shaft leading to the hole 72 is angled at an air inlet shaft angle 140 (FIG. 6C), which in the preferred embodiment is angled 45° relative to the central axis of the nozzle 7. The gas exit 74 of the air channels 71 and fluid exit 75 of the liquid channel 70 converge at the aerosolization space 73 where the aerosolization occurs. FIG. 6D shows a magnified view of the aerosolization space 73 of Detail A in FIG. 6C. The aerosolizing space 73 is defined between the fluid exit 75 at the outlet of the liquid jet nozzle 67 and the aerosol exit orifice 15 (FIG. 6D). The nozzle cap 68 circumferentially covers the tip of the liquid jet nozzle tip 67, including the aerosolization space 73 and fluid exit 75. The aerosol output characteristics are optimized by lengthening or shortening the liquid nozzle length 143, which runs from the start of liquid jet nozzle tip 67 to the fluid exit 75. The aerosols generated in the aerosolization space 73 are expelled through the aerosol exit orifice 15 into the aerosol chamber 10.

FIG. 7 shows an assembly including a chamber, cone, concentrator, and bidirectional valve. This assembly comprises a nozzle 7, a pedestal 87, an aerosol chamber 10, a cone 89, a concentrator 105, and a bidirectional valve assembly 130. The aerosol chamber 10 comprises an aerosol chamber input end 79 and an aerosol chamber output end 80. The aerosol chamber 10 houses the nozzle 7 and the counterflow tube 8. The nozzle 7 is inserted from the backside of the chamber 10. In a preferred embodiment, the chamber 10 may additionally include a cone 89 having a cone input end 93 having larger diameter and a cone output end 94 having a smaller diameter. The cone input end 93 may connect with the aerosol chamber output end 80, and the cone output end 94 may connect with the concentrator input end 117. In this configuration, the aerosol chamber 10 is effectively extended such that the aerosol chamber output end 80 and cone output end 94 are one and the same. In another embodiment, the chamber 10 and concentrator 105 may be configured to allow the aerosol chamber output end 80 to directly connect to the concentrator input end 117. The aerosol chamber 10 may include three annuli surrounding the nozzle barrel 66, specifically a first O-ring annulus 81, an air annulus 82, and a second O-ring annulus 83. The air annulus 82 supplies air to the air channels 71 in the nozzle barrel 66. The first and second O-ring annuli 81, 83 are disposed on opposite sides of the air annulus 82, and house O-rings.

In one configuration (as shown in FIG. 7C), a female pneumatic quick connect is threaded on the back of the chamber 10 for supplying air to the nozzle 7 and the counterflow tube 8 through a common port 84. The access hole 85 for the air annulus 82 for nozzle 7 may be plugged using a grub screw. In an alternate configuration (as shown in FIG. 2), the counterflow tube 8 and the nozzle 7 may have independent sources of compressed air supply, and accordingly include separate ports. The compressed air may be supplied using respective male quick connect pneumatic connectors for the nozzle 7 and the counterflow tube 8. The access hole 85 for the air annulus 82 may be plugged using a grub screw. The chamber 10 may further comprise two or more ribs 86 configured to mount the chamber 10 onto a pedestal 87. The pedestal 87 may include matching slots 88 configured to interface with the ribs 86. The structure of the pedestal 87 and its slots 88 are structured to enable the chamber 10 to firmly click onto the pedestal 87 for easy mounting and dismounting. For focusing the generated aerosol, a cone 89 may optionally be attached to the aerosol chamber output end 80 via a lip seal 90. The chamber 10 may further include a small drain hole 91 located at the bottom of the chamber 10 for draining liquid deposited on the inside

walls of the chamber 10 and/or cone 89. Liquid draining through the small drain hole 91 may be deposited into an inbuilt reservoir 92 located in the pedestal 87. The gas flow from the counterflow tube 8 opposes and reduces aerosol velocity emanating from the nozzle 7, thereby creating a virtual baffle. Disposed downstream from the aerosol chamber 10 is concentrator 105 including an input tube 109, an output tube 110, and an exhaust port 111. Downstream of the concentrator 105 is the bidirectional valve assembly 130 including the bidirectional valve assembly input 131, bidirectional valve assembly output 139, expiration port 137 which is shown in FIG. 7C in a closed configuration blocked by cylindrical disc 132.

FIG. 8 shows a concentrator have a cross-slit, in the following named a cross concentrator 105 shown in FIG 8A, which comprises an input housing part 106 and an output housing part 107. The input housing part 106 comprises a patterned mold 108 configured to connect with an input tube 109. Similarly, the output housing part 107 is configured to connect with an output tube 110. The input tube 109 may include an input tube entrance port 119, for instance having a circular cross-section as in the shown embodiment, but could alternatively square, polygonal, oval or of any other suitable shape, and an input tube exit port 120 having the shape of a cross-slit, wherein the cross-sectional shape of the input tube 109 transitions from said non-cross-slit-shape at the input tube entrance port 119 to a cross-slit-shape at the input tube exit port 120. The cross-slit shape preferably includes two linear slots crossing each other at a 90° angle, but alternative any other angle is possible. Also, the crossing slits do not necessarily need to be linear, although this is a preferred shape from both a manufacturing standpoint as well as an alignment standpoint with a corresponding output tube cross-slit. The output tube 110 may include an output tube entrance port 121 and an output tube exit port 122, wherein the cross-sectional shape of the output tube 110 transitions between the output tube entrance port 121 and an output tube exit port 122. The output tube entrance port may have a cross-slit-shape corresponding to the cross-slit of the input tube, and may be aligned therewith. As shown in FIG. 8D, the input tube 109 may converge from the input tube entrance port 119 to the input tube exit port 120, such that the input tube entrance port 119 has a greater cross-sectional area than that of the input tube exit port 120. Conversely, the output tube 110 may diverge from the output tube entrance port 121 to the output tube exit port 122, such that the output tube entrance port 121 has a lesser cross-sectional area than that of the output tube exit port 122. The input tube exit port 120 and output tube entrance port 121 may be disposed along a joint longitudinal axis and spaced apart by a gap 123.

Diverging of the input tube is optional but may be preferred for increasing the aerosol velocity through the cross-slit and therefore the momentum of the aerosol particles, resulting in a higher particle concentration rate. Converging of the output tube is likewise optional but preferred for reducing the velocity of the aerosol flow for a smoother for inhalation action and distribution of the aerosol particles. In lieu of converging/diverging profiles within the input/output tubes, a similar effect could also be accomplished by including additional components with similar profiles connected upstream/downstream of the input/output tubes. In this context, converging is to be understood as reducing the total cross-section of the lumen in the input tube along the direction of aerosol flow, while diverging is to be understood as increasing the total cross-section of the lumen in the output tube along with the direction of flow.

FIG. 8B shows the exploded view of the concentrator assembly. The output housing part 107 may include an exhaust port 111 for venting dilution gas. The housing 106, 107 may share a joint longitudinal axis with the input tube 109 and the output tube 110. This longitudinal axis is also the axis of the aerosol flow and runs through the center of the cross-slit, which is the point of intersection of the linear slits. The plenum 124 may be substantially encompassed by either the input housing part 106 or the output housing part 107. The housing part not encompassing the plenum 124 may be essentially disc-shaped, whereas the housing part substantially encompassing the plenum 124 may also include the exhaust tube 111 extending essentially radially in a transverse direction with respect to said longitudinal axis. The input tube 109 and output tube 110 may have radial sizes transverse to the longitudinal axis that are less than a third of a radial size of the plenum 124 transverse to said longitudinal axis. The exhaust port 111 may be oriented perpendicular to the longitudinal axis of aerosol flow between the concentrator input end 117 and concentrator output end 118, as also defined by the cross-section E-E shown in FIG. 8C. A pressure relief valve may be connected to the exhaust tube 111 for keeping a constant pressure within and across the concentrator 105, including at the output tube exit port 122. Both the input housing part 106 and the output housing part 107 may include lobes 112 and corresponding lobe molds 113 for alignment. The input housing part 106 and the output housing part 107 may be connected via a lip seal 114. The housing 106, 107 may encompass a plenum 124 defined by a void space surrounding and encompassing the input tube 109 and output tube 110, preferably in the shape of an annulus but alternatively could be any other shape that creates sufficient space around the gap 123 for receiving the

exhaust aerosol of low particle concentration without significant pressure drop, such that the overall pressure drop through the concentrator, and therefore for the entire system, is kept low. The plenum 124 may be connected to the exhaust port 111. The concentrator assembly may include a concentrator input mating surface 115 and a concentrator output mating surface 116 (shown in FIG. 8D) respectively corresponding to the concentrator input end 117 and the concentrator output end 118 through which the respirable aerosol flows. The concentrator input mating surface 115 may be configured to facilitate easy attachment with the cone 89 without necessitating fasteners.

FIG. 9 shows an Aerosol delivery respiratory support assembly comprising the bidirectional valve assembly 130 shown in FIG 9A enables functionality of the aerosol delivery respirator support 9. In one embodiment, the bidirectional valve assembly input 131 may connect with the cone output end 94 of the cone 89. In another embodiment the system includes a concentrator 105, the bidirectional valve assembly input 131 may connect with the concentrator output end 118 of the concentrator 105. A cylindrical disc 132 is included inside the bidirectional valve assembly 130. A pivot pin 133 is inserted through a hole in a sidewall of the bidirectional valve assembly 130 and connects to the disc 132 by interfacing with a set screw 134 located on the disc 132. These elements and their interactions are shown in an exploded view in FIG. 9B. As seen in FIG 9D, the bidirectional valve assembly 130 includes an annular aerosol delivery channel port 136 extending between a bidirectional valve assembly input 131 and a bidirectional valve assembly output 139. The upper wall of the aerosol delivery channel port 136 includes a first seat 135 against which the disc 132 butts up against when in a vertical position, thereby inhibiting further counterclockwise rotation. The lower wall includes a second seat 138 termination a distance from the pin 133 such that the disc 132 is simply supported when in a horizontal position, as shown in FIG 9D. The pin 133 may be actuated using a reciprocating pneumatic actuator 43 driven by the 5/2-way solenoid valve 29. When actuated by the pneumatic actuator 43, the pin 133 may rotate the disc 132 90 degrees to switch between open and closed positions. FIG 9D shows the bidirectional valve assembly in an open position, wherein the disk 132 seats horizontally within the second seat 138 such that the aerosol delivery channel port 136 is open and the expiration port 137 is closed. In a closed position, the disc 132 seats vertically within the first seat 135 such that the aerosol delivery channel port 136 is blocked and the expiration port 137 is opened. In one embodiment of

the invention, the bidirectional valve assembly output 139 may be configured to attach to an endotracheal tube (not pictured) for remote aerosol delivery.

FIGs. 10-14 demonstrate some results achieved by the system according to the invention with respect to the particle size distribution over the liquid flow rate of the liquid to be aerosolized, showing graphs for viscosities of 4 cP, 11 cP and 21 cP for the aerosolized liquid for a variety of nozzles of different nozzle exit orifice diameters, aerosolizing gases and system pressures.

FIG. 10 shows plots of flow rate (ranging from 0.75 ml/min to 3.5 ml/min) versus particle size (Dv 50 in units of μm) for three different concentrations of aqueous polyvinylpyrrolidone (PVP) with a system using compressed air, a system pressure of 60 psi, and a nozzle exit orifice diameter of 500 μm. The three different concentrations (by weight) of aqueous PVP solutions were 8%, 14% and 19%, and resulted in respective solution viscosities of 4, 11 and 21 cP. The 8% concentration solution is denoted by square plot points with a solid trendline, the 14% concentration solution is denoted by circular plot points with a dashed trendline, and the 19% concentration solution is denoted by triangular plot points with a dotted trendline. When the PVP solutions were aerosolized by AeroPulsR system at liquid pressure of 60 psi, the particle sizes of aerosols were found to be related to (i) PVP concentrations, (ii) the flow rates of the liquids, and (iii) the type of compressed gas used. From the flow rate ranging from 0.75 ml/min to 3.5 ml/min for each solution, the majority of the Dv 50 values of the aerosols were under 5 μm, except in one test where 8% PVP solution was aerosolized at 3.5 ml/min and compressed air was used. Meanwhile, smaller aerosols were obtained from a solution with higher PVP concentrations at the same flow rate.

FIG. 11 shows a plot for the same parameters as in FIG. 10, except substituting compressed heliox (a mixture of 80% helium and 20% oxygen) for compressed air to investigate the effect of compressed heliox on the particle size. Accordingly, aerosolization is conducted with identical settings mentioned previously with compressed air. A notable decrease in the particle sizes is observed with compressed heliox, when compared with compressed air.

FIG. 12 shows a plot for substantially the same parameters as in FIG. 10, except at a reduced system pressure of 50 psi. For obtaining this plot, the liquid pressure was reduced to 49 psi from 60 psi, and the aerosols were measured at a flow rate ranging from of 1 to 3 ml/min for PVP aqueous solution concentration (by weight) of 8%, 14%, and 19%. It was found that the overall aerosol size trend for different PVP solution concentration was similar to that observed for 60 psi liquid pressure. However, particle sizes for individual PVP concentrations were higher when compared with higher gas pressure.

FIG. 13 shows a plot for substantially the same parameters as in FIG. 10, except substituting the 500 µm nozzle with a 700 µm nozzle to investigate the size of the nozzle's exit orifice on aerosol particle size. With a system pressure of 60 psi, PVP aqueous solutions with concentrations of 8%, 14%, and 19% were aerosolized with a flow rate ranging from 1.5 to 4.5 ml/min. When compared with aerosol sizes achieved from 500 µm nozzle at 60 psi, it was found that under the same pressure and flow rate conditions, smaller aerosols from the same PVP solution can be generated from the 700 µm nozzle. The size of the nozzle exit orifice, therefore, can be modified to affect the size of the aerosol. For instance, at a flow rate of 3 ml/min, 21 cP PVP solution, and 500 µm nozzle exit orifice diameter, a Dv 50 of 4.2 µm resulted. However, using the same PVP solution with a nozzle exit orifice diameter of 700 µm resulted in a Dv 50 of 2.7 µm.

FIG. 14 shows a three-axis plot of flow rate (ranging from 0.75 ml/min to 3.5 ml/min) versus particle size (Dv 50 in µm) and span of H2O aerosol versus particle size (Dv 50 in µm) for H2O/compressed air and H2O/heliox. The particle size for the H2O/compressed air combination is denoted by hollow square plot points with a dashed trendline. The particle size for the H2O/heliox combination is denoted by hollow triangular plot points with a dotted trendline. The span for the H2O/compressed air combination is denoted by solid square plot points with a dot-dashed trendline. The span for the H2O/heliox combination is denoted by solid triangular plot points with a solid trendline. The AeroPulsR system generates aerosol particles with a narrow distribution. A narrow span in the range of 1.5 to 2 is observed for both compressed air and heliox.

FIGs. 15A–15D show two-axis plots of aerosol bolus intensity 145 versus time 146 in seconds. FIG. 15A shows the aerosol intensity variation 144 measured in arbitrary units of aerosol bolus intensity 145 when using the nozzle 7 in the present embodiment. The

aerosol bolus duration of 200 ms is generated at a frequency of 1 Hz. FIG. 15B shows a scaled view of a single bolus demonstrating a consistent aerosol generation within 200 ms using the nozzle 7 in the present embodiment. FIG. 15C shows the aerosol intensity variation 144 measured in arbitrary units of aerosol bolus intensity 145 when using the previous prior art nozzle. FIG. 15D shows a scaled view of a single bolus demonstrating inconsistent aerosol generation using the prior art nozzle.

A bolus intensity plot enables temporal measurement of ejecting aerosol boluses. The data for the plots was obtained by illuminated an aerosol bolus using high-intensity lights and the bolus ejection or cessation is captured using a high-speed camera at a given frame rate. The microcontroller 3 controls the solenoid valves which in turn controls the onset and termination of the compressed gas into the aerosolization space 73, ultimately turning the aerosol bolus on or off. There is a finite lag between the solenoid valve and aerosol activation/deactivation, which ideally is minimized to enable increased control over delivery. The bolus intensity plot enables measurement of this latency, namely the time period for the microcontroller 3 to send the signal and the time period for the aerosol bolus to be generated. An ideal bolus intensity plot has minimal lag between sending of a signal and expelling of a bolus, as well as minimal lag between sending of a signal and arresting the expelling of a bolus. Additionally, it is advantageous to maintain a consistent bolus intensity over time. This idealized plot is visually represented by a square wave. Evident from FIG. 15B, the presently disclosed nozzle is better able to maintain a consistent aerosol bolus activity level when the flow rate of the liquid is kept constant compared to the prior art nozzle represented in FIG. 15D, which exhibits a noticeable drop in aerosol bolus intensity. These measurements indicates that the presently disclosed nozzle exhibits improved performance over the prior art nozzle, producing advantageous effects of improved accuracy in maintaining the medicament delivery volume, and minimizing lag that may adversely affect bolus delivery in synchrony with the patient's breathing.

In the following, additional embodiments are described:

Embodiment 1. An aerosol concentrator 105 dividing an input aerosol of an input particle concentration into a concentrated respirable aerosol of an increased particle concentration that is higher than the input particle concentration and an exhaust aerosol of a lower

particle concentration that is lower than the input particle concentration, said concentrator 105 comprising:

an input tube 109 having a lumen and comprising:

an input tube entrance port 119 having an input tube entrance port cross-sectional shape differing from a cross-slit shape;

an input tube exit port 120 having a cross-slit shape, wherein the input tube entrance port cross-sectional shape transitions between the input tube entrance port 119 and the input tube exit port 120 to the cross-slit-shaped exit port cross-sectional shape;

an output tube 110 having a lumen and comprising:

an output tube entrance port 121 having a cross-slit-shaped cross-section, said output tube entrance port 121 being aligned with and spaced apart from the input tube exit port 120 by a gap 123 between the input tube exit port 120 and the output tube entrance port 121; and

an output tube exit port 122 wherein the output tube entrance port cross-sectional shape transitions between the output tube entrance port 121 and the output tube exit port 122 to an output tube exit port cross-sectional shape; and

a housing 106, 107 encompassing a plenum 124, said plenum 124 encompassing the gap 123 between the input tube 109 and the output tube 110, wherein the plenum 124 is connected to an exhaust port 111 through which an exhaust aerosol exits the plenum 124.

Embodiment 2. The aerosol concentrator 105 according to embodiment 1, wherein the input tube 109 converges from its input tube entrance port 119 to its input tube exit port 120 from an input tube entrance port cross-sectional area that is larger than an input tube exit port cross-sectional area.

Embodiment 3. The aerosol concentrator 105 according to embodiment 1 or 2, wherein the output tube 110 diverges from its output tube entrance port 121 to its output tube exit port 122 from an output tube entrance port cross-sectional area that is smaller than an output tube exit port cross-sectional area.

Embodiment 4. The aerosol concentrator 105 according to one of embodiments 1 – 3, wherein the input tube 109 and the output tube 110 have a collinear longitudinal axis and have radial sizes transverse to the longitudinal axis that are less than a third of a radial size of the plenum 124 transverse to said longitudinal axis.

Embodiment 5. The aerosol concentrator 105 according to one of embodiments 1 – 4, wherein the housing 106, 107 comprises an input housing part 106 holding the input tube 109, and an output housing part 107 holding the output tube 110 and the exhaust tube 111, and a lip seal 114 is provided between the input housing part 106 and the output housing part 107.

Embodiment 6. The aerosol concentrator 105 according to embodiment 5, wherein the housing 106, 107 shares the same collinear longitudinal axis with the input tube 109 and the output tube 110 and the plenum 124 is encompassed at least for the most part by either one of the input housing part 106 or the output housing part 107, while the other part of the output 107 or input housing 106, respectively, is essentially disc-shaped, with the housing part encompassing at least for the most part the plenum 124 also having the exhaust tube 111 which extends essentially radially in a transverse direction with respect to said longitudinal axis.

Embodiment 7. The aerosol concentrator 105 according to one of embodiments 1 – 6, wherein a pressure relief valve is connected to the exhaust tube 111 keeping the pressure within and across concentrator 105 and consequently at the output tube exit port 122 essentially constant.

Embodiment 8. The aerosol concentrator 105 according to one of embodiments 1 – 7, wherein the pressure at the output tube exit port 122 and the pressure at the exhaust port 111 are adjusted such that up to 80% of the volumetric flow rate of gas entering the input tube entrance port 119 exits the concentrator 105 via the exhaust port 111, while the majority of the aerosol particles in the remaining volumetric flow rate of gas exit the concentrator 105 via the output tube exit port 122.

Embodiment 9. The aerosol concentrator 105 according to one of embodiments 1 – 8, wherein the pressure within the input tube entrance port 119 is marginally higher than the pressure within the output tube exit port 122, and the pressure within the input tube entrance port 119 is higher than the pressure in the plenum 124.

Embodiment 10. The aerosol concentrator 105 according to one of embodiments 1 – 9, wherein the concentrator 105 is designed to concentrate an input aerosol having fine

particles of a particle size distribution of 2 – 5 μm median mass aerodynamic diameter (MMAD) aerosols suspended in gas.

Embodiment 11. The aerosol concentrator 105 according to one of embodiments 1 – 10, wherein the concentrator 105 is designed to concentrate an aerosol using virtual impaction at a small positive pressure within and across concentrator 105 all the way to the output tube exit port 122 such that the concentrated respirable aerosol can be delivered to the patient at the small positive pressure without the use of pumps to remove the exhausted gas.

Embodiment 12. The aerosol concentrator 105 according to one of embodiments 1 – 11, further comprising a concentrator output end 118 disposed immediately downstream of the output tube exit port 122, said concentrator output end 118 configured to be removably coupled to a bidirectional valve assembly 130.

Embodiment 13. The aerosol concentrator 105 according to one of embodiments 1 – 12, further comprising a concentrator input end 117 disposed immediately upstream of the input tube entrance port 119, said concentrator input end 117 configured to be removably coupled to an output cone 89.

Embodiment 14. The aerosol concentrator 105 according to one of embodiments 1 – 13, wherein the input tube entrance port cross-sectional shape is substantially circular.

Embodiment 15. The aerosol concentrator 105 according to one of embodiments 1 – 14, said concentrator 105 configured to achieve at least a twofold increase in aerosol concentration while maintaining substantially the same mass of the aerosolized drug.

Embodiment 16. The aerosol concentrator 105 according to one of embodiments 1 – 15, wherein the gap 123 is configured such that a majority of the aerosols having diameters less than 1 μm travel through the sides of the gap 123 and exit the concentrator 105 through the exhaust port 111 prior to reaching the output tube entrance port 121, while permitting higher inertial aerosol particles having diameters of 1 μm or greater to pass into the output tube entrance port 121.

Embodiment 17. The aerosol concentrator 105 according to one of embodiments 1 – 16, wherein the gap 123 between the input tube exit port 120 and the output tube entrance port 121 spans a length between 1.5 – 2.5 mm.

Embodiment 18. The aerosol concentrator 105 according to one of embodiments 1 – 17, wherein the concentrator 105 is configured to produce a respirable volumetric flow rate including at least 40% of aerosol particles at a concentrator output end 118 disposed immediately downstream of the output tube exit port 122, and an exhaust volumetric flow rate including 50% or less of the aerosol particles at the exhaust port 111.

Embodiment 19. The aerosol concentrator 105 according to one of embodiments 1 – 18, wherein the cross-slit shape of the input tube exit port 120 is defined by a first input tube exit port slit and a second input tube exit port slit formed perpendicular to the first input tube exit port slit; and the cross-slit shape of the output tube entrance port 121 is defined by a first output tube entrance port slit and a second output tube entrance port slit formed perpendicular to the first output tube entrance port slit.

Embodiment 20. The aerosol concentrator 105 according to embodiment 19, wherein the width of the first and second input tube exit port slits is narrower than the width of the first and second output tube entrance port slits.

Embodiment 21. The aerosol concentrator 105 according to embodiment 19 or 20, wherein the width of the first and second input tube exit port slits is 1 mm, and the width of the first and second output tube entrance port slits is 1.5 mm.

Embodiment 22. The aerosol concentrator 105 according to one of embodiments 19 – 21, wherein the input volume flow rate to be concentrated is proportional to at least one of: (i) the sum of the lengths of the first and second input tube exit port slits, and (ii) the sum of the lengths of the first and second output tube entrance port slits.

Embodiment 23. The aerosol concentrator 105 according to one of embodiments 19 – 22, wherein the sum of the lengths of the first and second input tube exit port slits is identical to the sum of the lengths of the first and second output tube entrance port slits.

Embodiment 24. The aerosol concentrator 105 according to one of embodiments 19 – 23, wherein the sum of the lengths of the first and second input tube exit port slits is equal to 26 mm; and the sum of the lengths of the first and second output tube entrance port slits is equal to 26 mm.

Embodiment 25. The aerosol concentrator 105 according to one of embodiments 1 – 24, wherein the aerosol concentrator 105 is configured to concentrate input aerosol having an input volume flow rate of 30 l/min.

The following is a list of reference numerals as shown in the drawings:

console 1
patient/clinician interface 2
microcontroller 3
hardware controller 4
internal hardware 5
liquid dispenser 6
aerosol nozzle 7
counter flow tube 8
aerosol delivery respiratory support 9
aerosol chamber 10
liquid supply line 11
gas supply line 12
gas supply line 13
counterflow gas tube supply line 14
aerosol exit orifice 15
counterflow gas tube exit opening 16
high pressure source 20
system pressure regulator 21
liquid pressure regulator 22
liquid container 23
3-2 way solenoid valve V1 24
nozzle gas regulator 25
three-way solenoid valve V2 26

regulator R3 27

3-2-way solenoid valve V3 28

5-2-way solenoid valve V4 29

two pneumatic lines 31

dispenser cap 41

dispenser mount 42

pneumatic actuator 43

cut threads 44

half turn threads 45

threaded holes 46

threaded port 47

hollow channel 48

cantilever clips 50

slots 51

keys 52

sliding tracks 53

through channel 56

O-rings 57

liquid delivery port 58

nozzle liquid input 60

knob 65

barrel 66

liquid jet nozzle tip 67

nozzle cap 68

threads 69

liquid channel 70

air channels 71

hole 72

aerosolization space 73

gas exit 74

fluid exit 75

aerosol chamber input end 79

aerosol chamber output end 80

first O-ring annulus 81

air annulus 82
second O-ring annulus 83
common port 84
access port 85
ribs 86
pedestal 87
matching slots 88
cone 89
lip seal 90
small drain hole 91
inbuilt reservoir 92
cone input end 93
cone output end 94
cross concentrator 105
input housing part 106
output housing part 107
patterned mold 108
input tube 109
output tube 110
exhaust port 111
lobes 112
lobe molds 113
lip seal 114
concentrator input mating surface 115
concentrator output mating surface 116
concentrator input end 117
concentrator output end 118
input tube entrance port 119
input tube exit port 120
output tube entrance port 121
output tube exit port 122
gap 123
plenum 124
bidirectional valve assembly 130

bidirectional valve assembly input 131

cylindrical disc 132

pivot pin 133

set screw 134

first seat 135

aerosol delivery channel port 136

expiration port 137

second seat 138

bidirectional valve assembly output 139

air inlet shaft angle 140

air channel diameter 141

liquid channel diameter 142

liquid nozzle length 143

aerosol bolus intensity variation 144

aerosol bolus intensity 145

time 146

electronic control and interface module (ECIM) 147

male luer connector 148

CLAIMS

1. An aerosol concentrator (105) dividing an input aerosol of an input particle concentration into a concentrated respirable aerosol of an increased particle concentration that is higher than the input particle concentration and an exhaust aerosol of a lower particle concentration that is lower than the input particle concentration, said concentrator (105) comprising:

an input tube (109) having a lumen and comprising:

an input tube entrance port (119) having an input tube entrance port cross-sectional shape differing from a cross-slit shape;

an input tube exit port (120) having a cross-slit shape, wherein the input tube entrance port cross-sectional shape transitions between the input tube entrance port (119) and the input tube exit port (120) to the cross-slit-shaped exit port cross-sectional shape;

an output tube (110) having a lumen and comprising:

an output tube entrance port (121) having a cross-slit-shaped cross-section, said output tube entrance port (121) being aligned with and spaced apart from the input tube exit port (120) by a gap (123) between the input tube exit port (120) and the output tube entrance port (121); and

an output tube exit port (122) wherein the output tube entrance port cross-sectional shape transitions between the output tube entrance port (121) and the output tube exit port (122) to an output tube exit port cross-sectional shape; and

a housing (106, 107) encompassing a plenum (124), said plenum (124) encompassing the gap (123) between the input tube (109) and the output tube (110), wherein the plenum (124) is connected to an exhaust port (111) through which an exhaust aerosol exits the plenum (124).

2. The aerosol concentrator (105) according to claim 1, wherein the input tube (109) converges from its input tube entrance port (119) to its input tube exit port (120) from an input tube entrance port cross-sectional area that is larger than an input tube exit port cross-sectional area.

3. The aerosol concentrator (105) according to claim 1, wherein the output tube (110) diverges from its output tube entrance port (121) to its output tube exit port (122) from an output tube entrance port cross-sectional area that is smaller than an output tube exit port cross-sectional area.

4. The aerosol concentrator (105) according to claim 1, wherein the input tube (109) and the output tube (110) have a collinear longitudinal axis and have radial sizes transverse to the longitudinal axis that are less than a third of a radial size of the plenum (124) transverse to said longitudinal axis.

5. The aerosol concentrator (105) according to claim 1, wherein the housing (106, 107) comprises an input housing part (106) holding the input tube (109), and an output housing part (107) holding the output tube (110) and the exhaust tube (111), and a lip seal (114) is provided between the input housing part (106) and the output housing part (107).

6. The aerosol concentrator (105) according to claim 5, wherein the housing (106, 107) shares the same collinear longitudinal axis with the input tube (109) and the output tube (110) and the plenum (124) is encompassed at least for the most part by either one of the input housing part (106) or the output housing part (107), while the other part of the output (107) or input housing (106), respectively, is essentially disc-shaped, with the housing part encompassing at least for the most part the plenum (124) also having the exhaust tube (111) which extends essentially radially in a transverse direction with respect to said longitudinal axis.

7. The aerosol concentrator (105) according to claim 5, wherein a pressure relief valve is connected to the exhaust tube (111) keeping the pressure within and across concentrator (105) and consequently at the output tube exit port (122) essentially constant.

8. The aerosol concentrator (105) according to claim 1, wherein the pressure at the output tube exit port (122) and the pressure at the exhaust port (111) are adjusted such that up to

80% of the volumetric flow rate of gas entering the input tube entrance port (119) exits the concentrator (105) via the exhaust port (111), while the majority of the aerosol particles in the remaining volumetric flow rate of gas exit the concentrator (105) via the output tube exit port (122).

9. The aerosol concentrator (105) according to claim 1, wherein the pressure within the input tube entrance port (119) is marginally higher than the pressure within the output tube exit port (122), and the pressure within the input tube entrance port (119) is higher than the pressure in the plenum (124).

10. The aerosol concentrator (105) according to claim 1, wherein the concentrator (105) is designed to concentrate an input aerosol having fine particles of a particle size distribution of 2 – 5 μm median mass aerodynamic diameter (MMAD) aerosols suspended in gas.

11. The aerosol concentrator (105) according to claim 1, wherein the concentrator (105) is designed to concentrate an aerosol using virtual impaction at a small positive pressure within and across concentrator (105) all the way to the output tube exit port (122) such that the concentrated respirable aerosol can be delivered to the patient at the small positive pressure without the use of pumps to remove the exhausted gas.

12. The aerosol concentrator (105) according to claim 1, further comprising a concentrator output end (118) disposed immediately downstream of the output tube exit port (122), said concentrator output end (118) configured to be removably coupled to a bidirectional valve assembly (130).

13. The aerosol concentrator (105) according to claim 1, further comprising a concentrator input end (117) disposed immediately upstream of the input tube entrance port (119), said concentrator input end (117) configured to be removably coupled to an output cone (89).

14. The aerosol concentrator (105) according to claim 1, wherein the input tube entrance port cross-sectional shape is substantially circular.

15. The aerosol concentrator (105) according to claim 1, said concentrator (105) configured to achieve at least a twofold increase in aerosol concentration while maintaining substantially the same mass of the aerosolized drug.

16. The aerosol concentrator (105) according to claim 1, wherein the gap (123) is configured such that a majority of the aerosols having diameters less than 1 μm travel through the sides of the gap (123) and exit the concentrator (105) through the exhaust port (111) prior to reaching the output tube entrance port (121), while permitting higher inertial aerosol particles having diameters of 1 μm or greater to pass into the output tube entrance port (121).

17. The aerosol concentrator (105) according to claim 16, wherein the gap (123) between the input tube exit port (120) and the output tube entrance port (121) spans a length between 1.5 – 2.5 mm.

18. The aerosol concentrator (105) according to claim 16, wherein the concentrator (105) is configured to produce a respirable volumetric flow rate including at least 40% of aerosol particles at a concentrator output end (118) disposed immediately downstream of the output tube exit port (122), and an exhaust volumetric flow rate including 50% or less of the aerosol particles at the exhaust port (111).

19. The aerosol concentrator (105) according to claim 1, wherein the cross-slit shape of the input tube exit port (120) is defined by a first input tube exit port slit and a second input tube exit port slit formed perpendicular to the first input tube exit port slit; and

the cross-slit shape of the output tube entrance port (121) is defined by a first output tube entrance port slit and a second output tube entrance port slit formed perpendicular to the first output tube entrance port slit.

20. The aerosol concentrator (105) according to claim 19, wherein the width of the first and second input tube exit port slits is narrower than the width of the first and second output tube entrance port slits.

21. The aerosol concentrator (105) according to claim 20, wherein the width of the first and second input tube exit port slits is 1 mm, and the width of the first and second output tube entrance port slits is 1.5 mm.

22. The aerosol concentrator (105) according to claim 19, wherein the input volume flow rate to be concentrated is proportional to at least one of: (i) the sum of the lengths of the first and second input tube exit port slits, and (ii) the sum of the lengths of the first and second output tube entrance port slits.

23. The aerosol concentrator (105) according to claim 22, wherein the sum of the lengths of the first and second input tube exit port slits is identical to the sum of the lengths of the first and second output tube entrance port slits.

24. The aerosol concentrator (105) according to claim 23, wherein the sum of the lengths of the first and second input tube exit port slits is equal to 26 mm; and

the sum of the lengths of the first and second output tube entrance port slits is equal to 26 mm.

25. The aerosol concentrator (105) according to claim 24, wherein the aerosol concentrator (105) is configured to concentrate input aerosol having an input volume flow rate of 30 l/min.

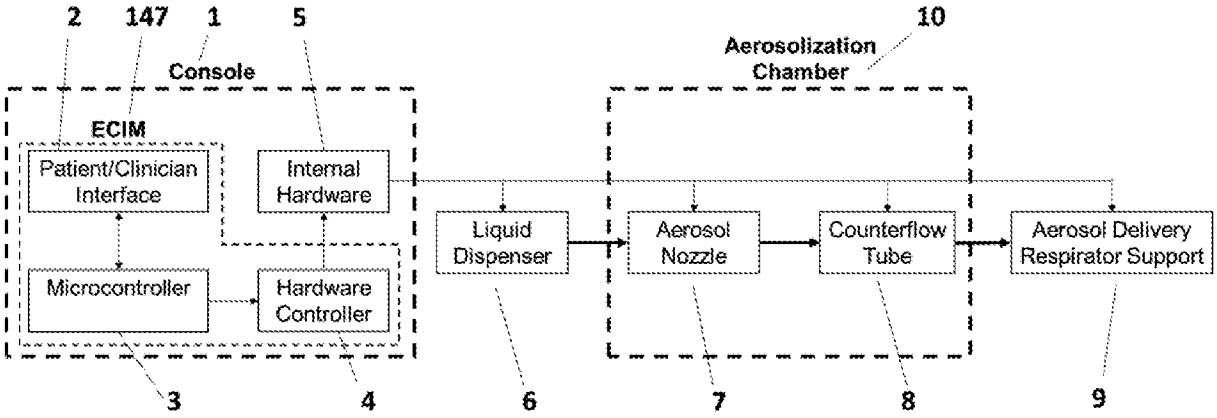
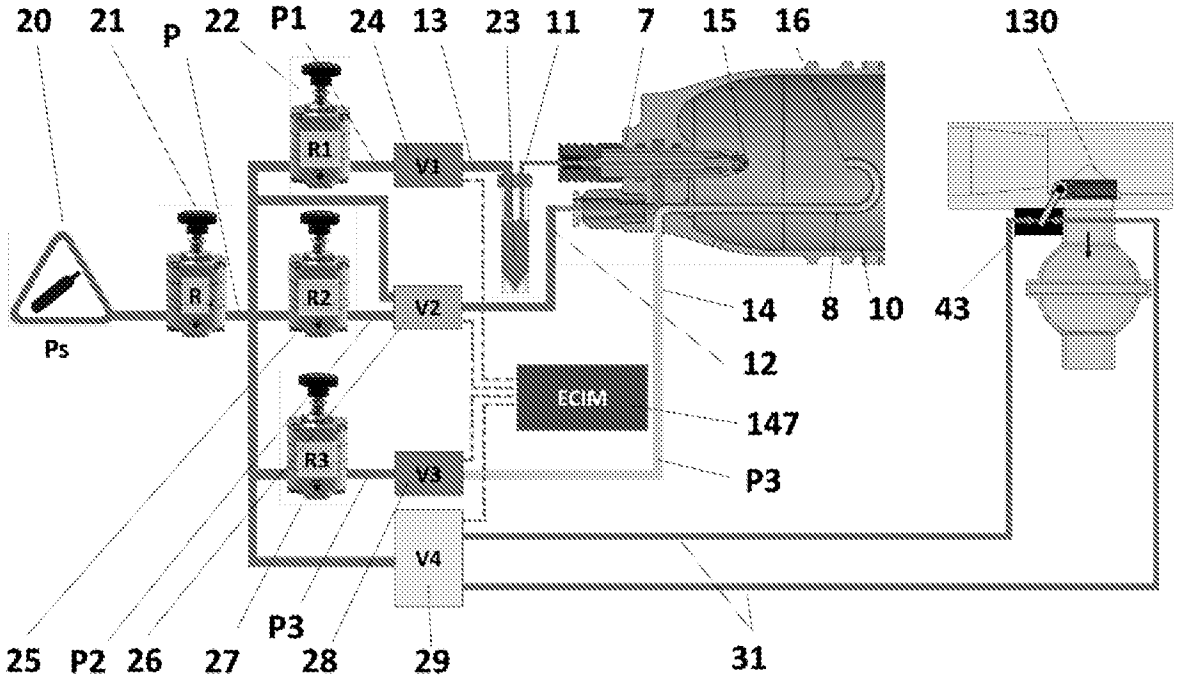

2
147
1
5
Console
ECIM
Patient/Clinician Interface
Internal Hardware
Microcontroller
Hardware Controller
3
4
10
Aerosolization Chamber
Liquid Dispenser
Aerosol Nozzle
Counterflow Tube
Aerosol Delivery Respirator Support
6
7
8
9

FIG 1


20
21
P
22
P1
24
13
23
11
7
15
16
130
R1
V1
R
R2
V2
Ps
14
8
10
43
12
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R3
V3
P3
V4
25
P2
26
27
P3
28
29
31

FIG 2

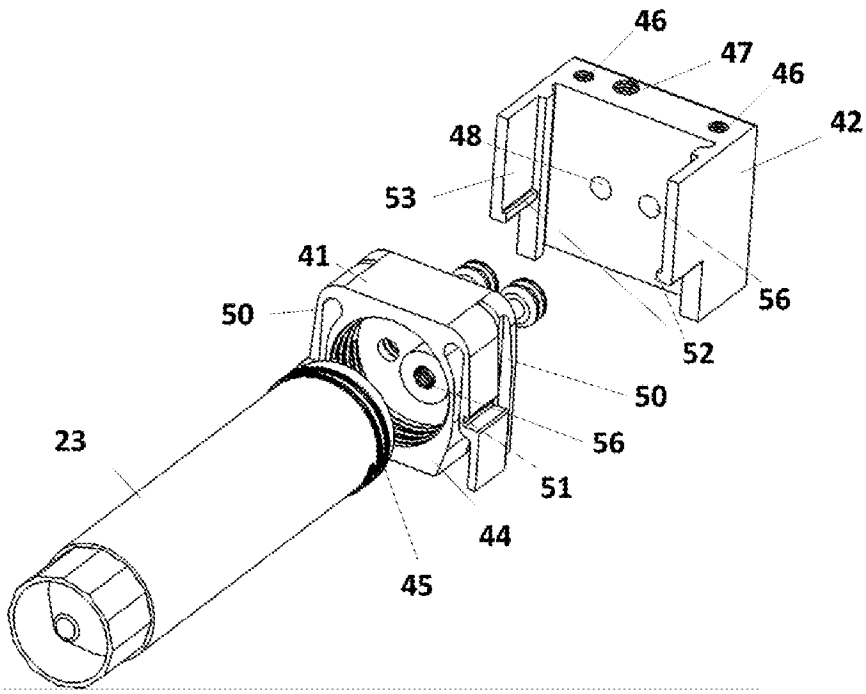


FIG 3

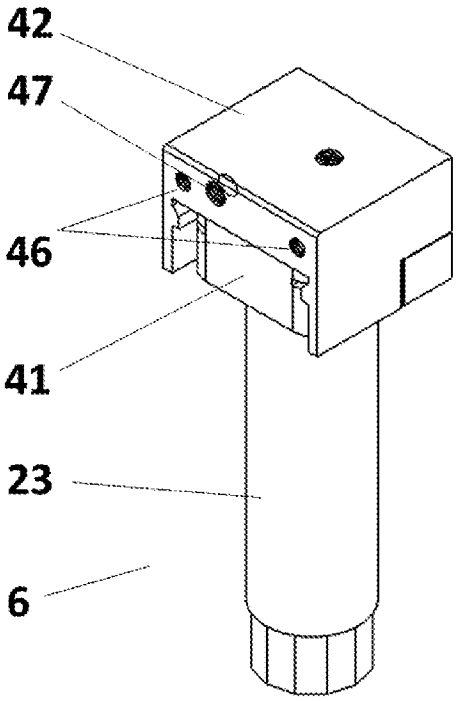


FIG 4A

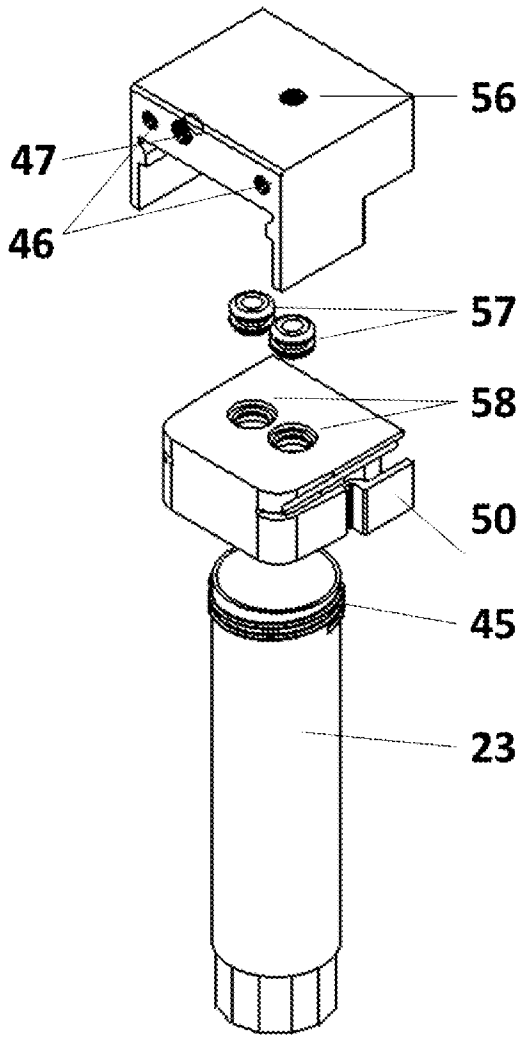


FIG 4B

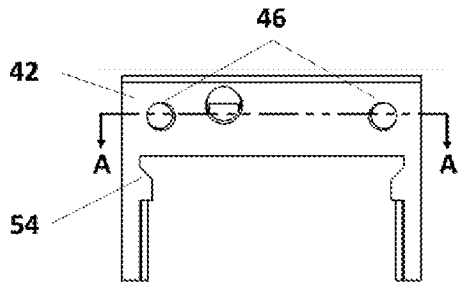


FIG 5A

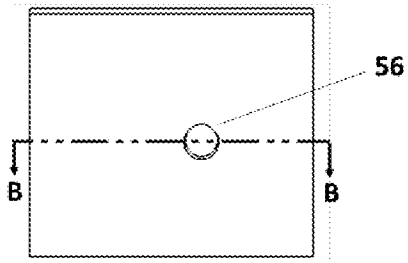


FIG 5C

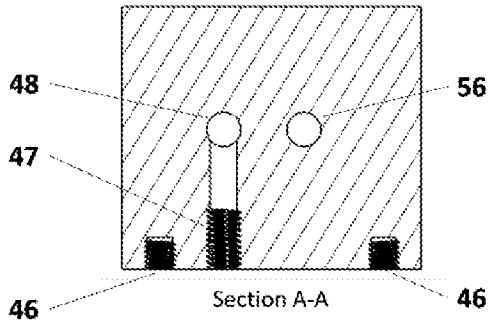


FIG 5B

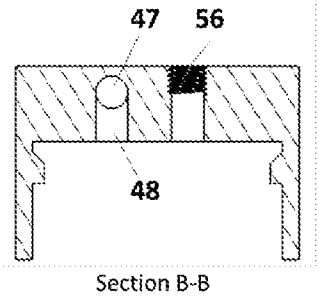


FIG 5D

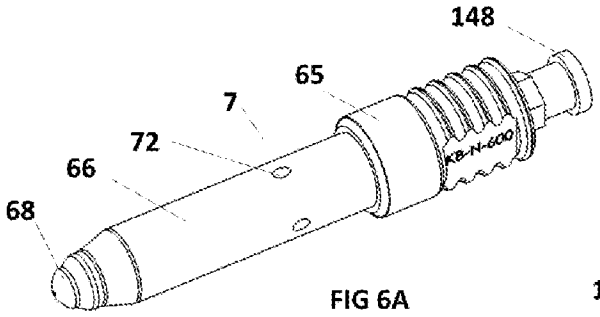


FIG 6A

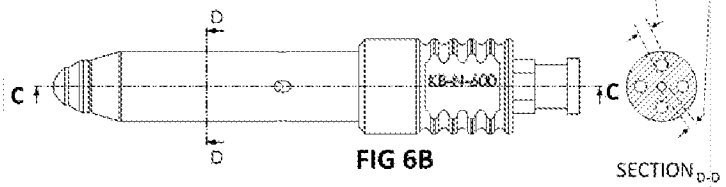
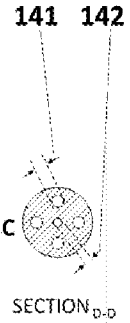


FIG 6B



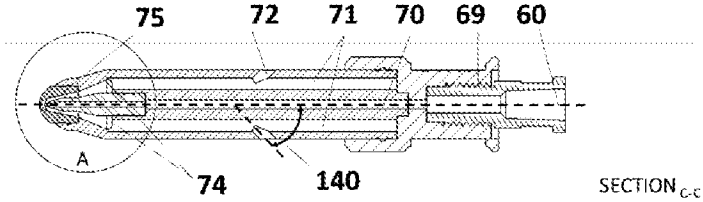
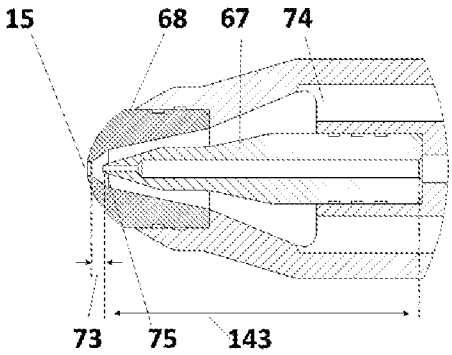


FIG 6C



DETAIL A

FIG 6D

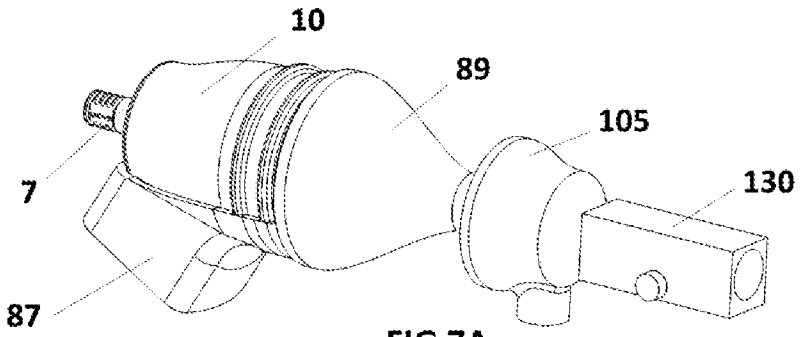


FIG 7A

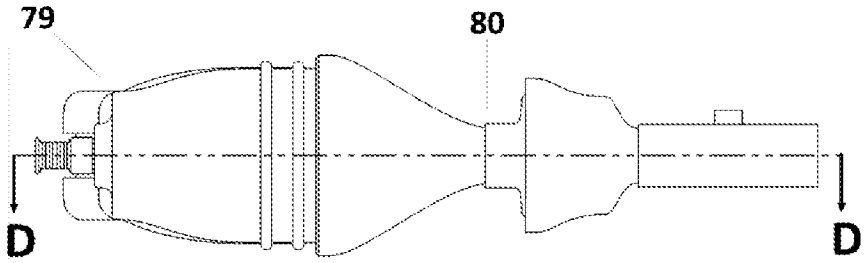
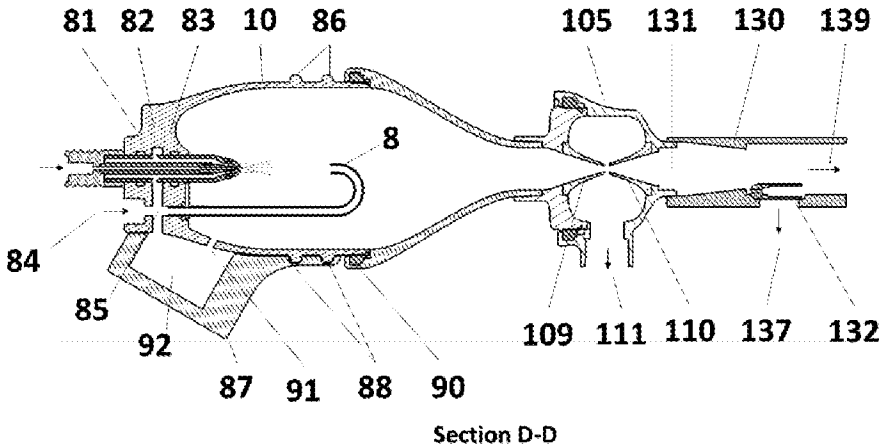


FIG 7B



Section D-D

FIG 7C

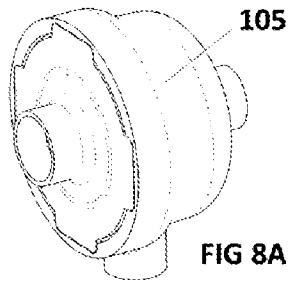


FIG 8A

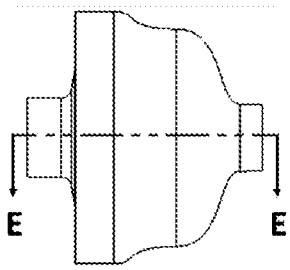


FIG 8C

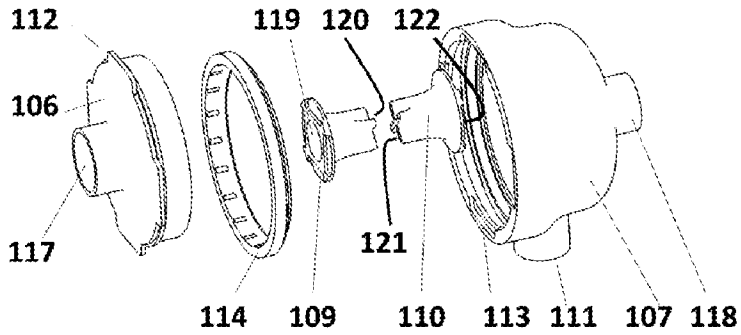


FIG 8B

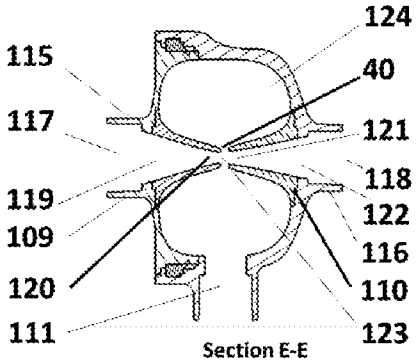


FIG 8D

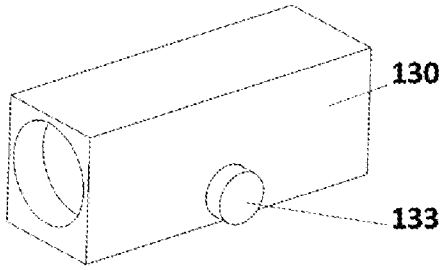


FIG 9A

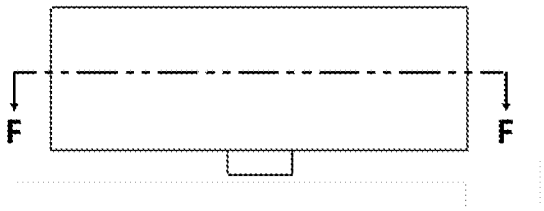


FIG 9C

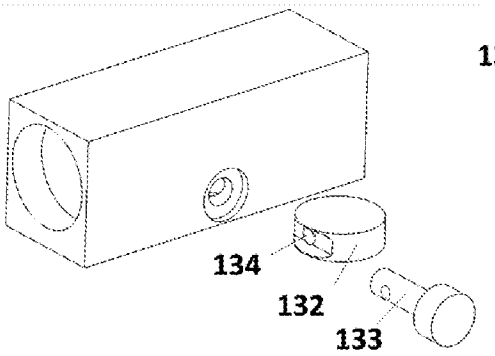
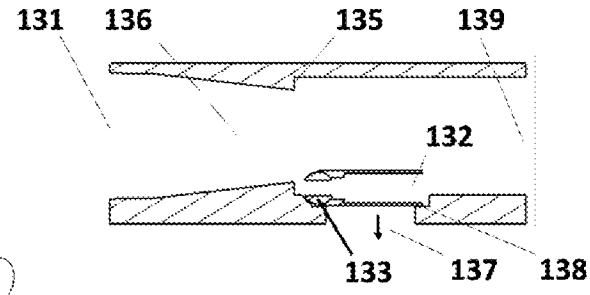


FIG 9B



Section F-F
FIG 9D

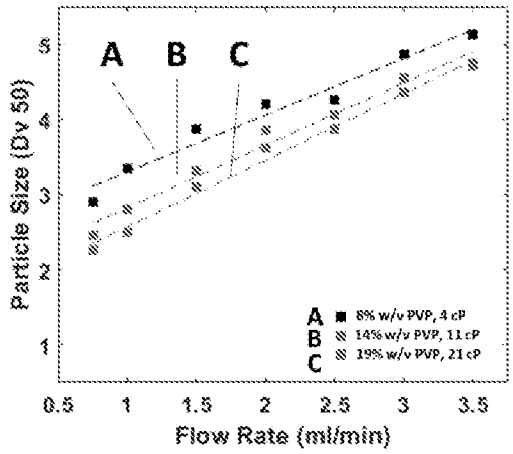


FIG 10

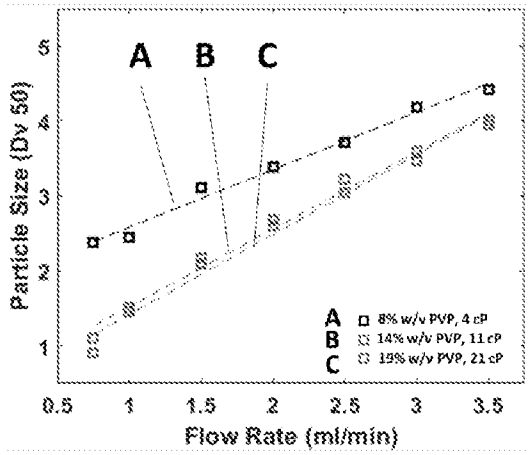


FIG 11

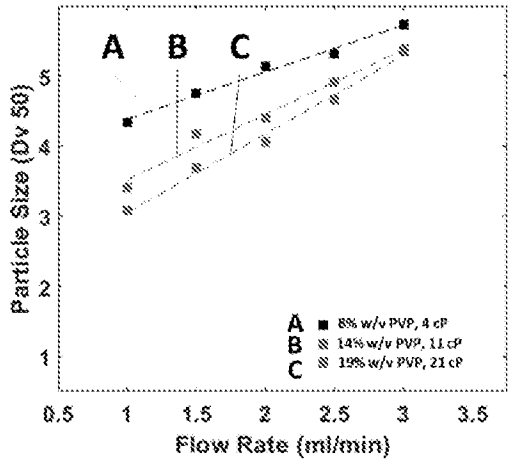


FIG 12

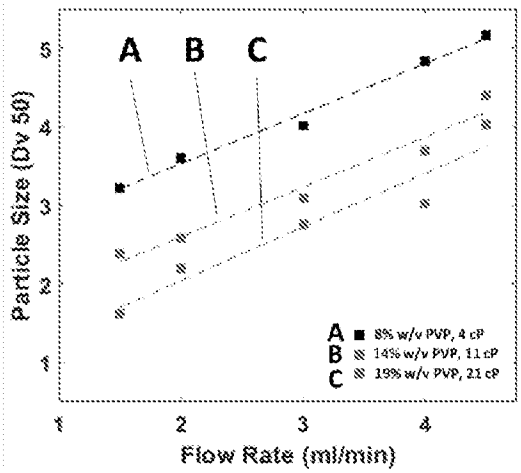


FIG 13

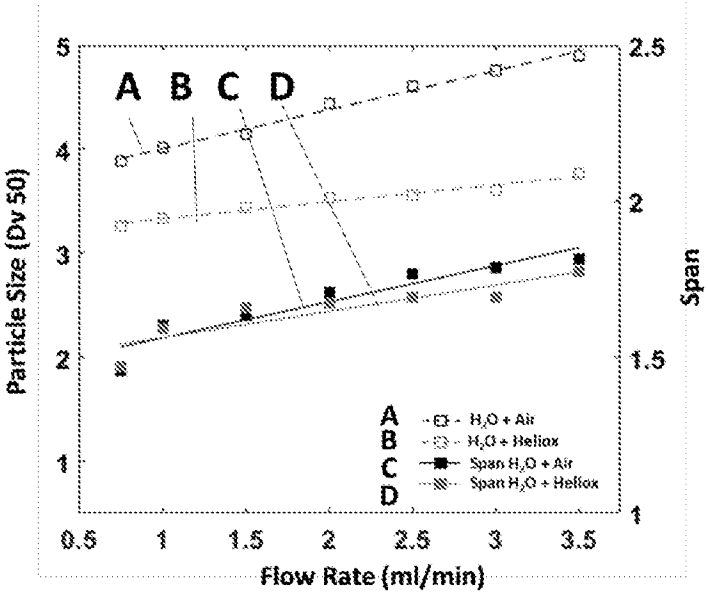

A B C D
Particle Size (Dv 50)
Span
Flow Rate (ml/min)
0.5
1
1.5
2
2.5
3
3.5
1
2
3
4
5
1
1.5
2
2.5
A
B
C
D
H2O + Air
H2O + Heliox
Span H2O + Air
Span H2O + Heliox

FIG 14

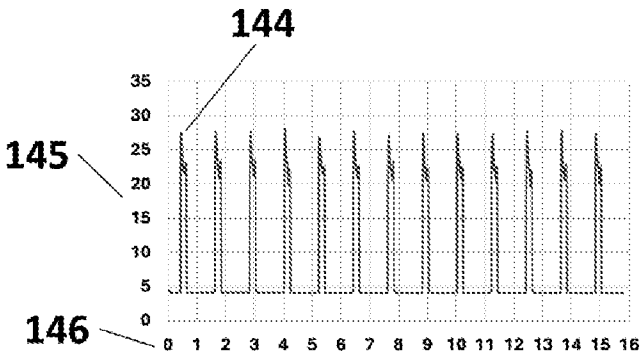


FIG 15A

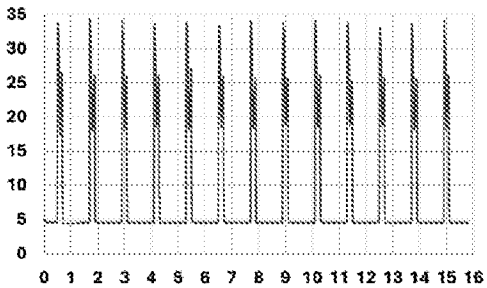


FIG 15C

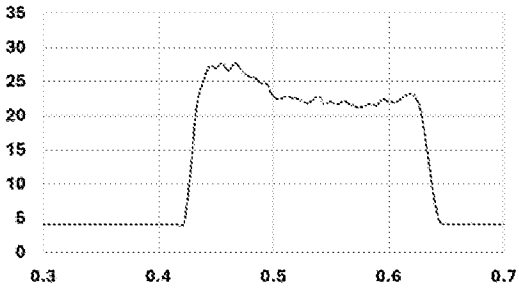


FIG 15B

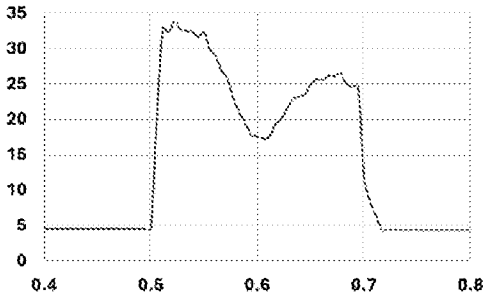


FIG 15D