GAS DISPENSER FOR DISPENSING ACCURATE DOSES OF THERAPEUTIC GAS FROM A RESERVOIR CONTAINING HIGHLY COMPRESSED THERAPEUTIC GAS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application Serial No. 61/350,417, filed on June 1, 2010, which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0002] Described here are devices for dispensing therapeutic gases to the nasal mucosa of a patient. More particularly, the dispensing devices include one or more components for regulating the gas flow and pressure from a hand-held dispenser for the safe, controlled, intranasal delivery of a pressurized therapeutic gas. Methods for intranasally delivering therapeutic gases to patients are also described.

BACKGROUND

[0003] A typical compressed gas pressure regulator incorporates a spring-loaded diaphragm mechanism that regulates the opening and closing of a gas discharge orifice. This mechanism can be calibrated manually to provide constant delivery pressure at any value within a designated range. After the desired delivery pressure is set, the regulator may open or close the gas discharge to maintain constant pressure. In turn, the flow rate may be controlled by the use of a separate restricting orifice or similar component. Many different pressure regulating and flow rate controlling features are commercially available. However, these known gas dispensers do not always dispense a therapeutic gas in an accurate and/or economical manner.

[0004] Accordingly, dispensers having mechanical and/or functional characteristics that help to optimize the dispensing of therapeutic gases or optimize the delivery of therapeutic gases to target tissues, e.g., the nasal mucosa, would be useful.

SUMMARY

[0005] Described here are devices and methods for dispensing therapeutic gases to the nasal mucosa of a patient.

[0005a] According to a first aspect, there is provided a device for dispensing a therapeutic gas to a patient comprising: a compressed gas cylinder, a first valve and a second valve, a first pressure regulator and a second pressure regulator, a measurement chamber that has a defined volume of therapeutic gas at a predetermined pressure set by the first pressure regulator, and a sequencing mechanism that is coupled to the first valve and the second valve, wherein the sequence mechanism alternately opens and closes the first valve and second valve, wherein the compressed gas cylinder is coupled to input of the first valve, and output of the first valve is coupled to input on the first pressure regulator, and output of the first pressure regulator is coupled to input of the second pressure regulator and to the measurement chamber, wherein output of the second pressure regulator is coupled to input of the second valve and output of the second valve is coupled to the patient, wherein the therapeutic gas passes from the compressed gas cylinder through the first pressure regulator to the measurement chamber, then the therapeutic gas passes from the measurement chamber through the second pressure regulator to provide the patient a constant volume of therapeutic gas. In general, the devices are configured to include a compressed gas cylinder, a first valve and a second valve, a first pressure regulator and a second pressure regulator, a measurement chamber that has a defined volume of therapeutic gas at a predetermined pressure set by the first pressure regulator, and a sequencing mechanism that is coupled to the first valve and the second valve. The sequence mechanism may alternately open and close the first valve and second valve. The aforementioned components may be viewed as being operatively connected to each other in a manner that dispenses consistent doses of a therapeutic gas to patients.

[0006] In some variations, the compressed gas cylinder is coupled to the input of the first valve, and output of the first valve is coupled to the input on the first pressure regulator, and output of the first pressure regulator is coupled to the input of the second pressure regulator and to the measurement chamber. Here output of the second pressure regulator may be coupled to input of the second valve and output of the second valve may be

coupled to the patient. In use, a therapeutic gas typically passes from the compressed gas cylinder through the first pressure regulator to the measurement chamber. The therapeutic gas then passes from the measurement chamber through the second pressure regulator to provide the patient a constant volume of a therapeutic gas.

[0007] Variations of the device may further include an orifice to control the rate of gas flow, wherein the output of the second valve is coupled to one end of the orifice and another end of the orifice is coupled to the patient. The sequence mechanism of the devices may comprise either a mechanical or an electronic apparatus.

[0008] With respect to the measurement chamber, this component of the device may store a volume of therapeutic gas at a controlled pressure of approximately 200 psi. The patient here may receive a constant flow rate of gas of approximately 0.5 standard liters per minute at a controlled pressure of approximately 1 atmosphere. The therapeutic gases that may be dispensed include without limitation, carbon dioxide, nitric oxide, oxygen, gaseous acids, helium, and combinations thereof.

[0009] Methods for intranasally delivering a therapeutic gas to a patient are also described herein.

[0009a] According to a second aspect, there is provided a method for delivering intranasally a therapeutic gas to a patient comprising the steps of: obtaining the above device, activating the sequence mechanism to open the first valve and close the second valve to allow the therapeutic gas to flow from the compressed gas cylinder to the measurement chamber, activating the sequence mechanism to close the first valve and open the second valve to allow the therapeutic gas to flow from the measurement chamber to the patient, wherein the patient receives the therapeutic gas at a constant flow rate and pressure. In general, the methods include the steps of obtaining a device comprising a compressed gas cylinder, a first valve and a second valve, a first pressure regulator and a second pressure regulator, a measurement chamber that has a defined volume of therapeutic gas at a predetermined pressure set by the first pressure regulator, and a sequencing mechanism that is coupled to the first valve and the second valve; activating the sequence mechanism to open the first valve and close the second valve to allow the therapeutic gas to flow from the compressed gas cylinder to the measurement chamber; and activating the sequence mechanism to close the first valve and open the second valve to allow the therapeutic gas to flow from the measurement chamber to the patient. The methods are devised so that the patient receives the therapeutic gas at a constant flow rate and pressure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] Fig. 1 schematically illustrates the components of an exemplary therapeutic gas dispenser.

[0011] Fig. 2 illustrates an exemplary flow rate performance of a therapeutic gas dispenser.

[0012] Fig. 3 illustrates the major subsystems of one variation of a therapeutic gas dispenser.

[0013] Fig. 4 shows a more detailed view of the dispenser in Fig. 3.

[0014] Fig. 5 depicts three layouts of common piston regulators.

[0015] Fig. 6 illustrates a diaphragm regulator analogous to Layout 2a of Fig. 5.

[0016] Fig. 7 shows a carbon dioxide phase diagram.

DETAILED DESCRIPTION

[0017] Described here are devices and methods for dispensing therapeutic gases to the nasal mucosa of a patient. The devices typically comprise a combination of a measurement chamber, pressure regulators and a sequencing mechanism that controls valves associated with the pressure regulators. More specifically, the devices are generally configured to include a compressed gas cylinder, a first valve and a second valve, a first pressure regulator and a second pressure regulator, a measurement chamber that has a defined volume of therapeutic gas at a predetermined pressure set by the first pressure regulator, and a sequencing mechanism that is coupled to the first valve and the second valve. When the

devices described herein are implemented in a hand-held dispenser, the hand-held dispenser may reliably deliver consistent doses of gas regardless of the unknown state and pressure of the therapeutic gas. An additional benefit of the herein described devices is that they may be constructed from inexpensive mechanical components and may be manufactured in a very compact form.

[0018] An exemplary device **100** is shown in Fig. 1. As shown, device **100** comprises:

1. A standard-sized pressure vessel or compressed gas cylinder **101** that may be filled with liquid or super-critical carbon dioxide or other therapeutic gas and a metallic seal that remains intact until the user activates the device.

2. A mechanism to attach and seal the cylinder to the device.

3. A mechanism for piercing the pressure vessel seal.

4. A filter **102** that prevents particles from passing from the cylinder into the device. The compressed gas cylinder **101** is coupled to the input of the filter **102** and the output of the filter **102** is coupled to the input of the first valve **103**.

5. A "primary" or first pressure regulator **104** that reduces the pressure of the carbon dioxide to a set value after it leaves the compressed gas cylinder **101**. The output of first valve **103** is coupled to the input of "primary" or first pressure regulator **104**.

6. A volumetric chamber or measurement chamber **108** that is filled with the gas at a controlled pressure set by the primary or first pressure regulator **104**. The measurement chamber **108** determines or has a defined volume of therapeutic gas at a predetermined pressure set by the first pressure regulator **104**.

7. A "secondary" or second pressure regulator **105** that reduces the pressure of the gas to a set value as it exits the measurement chamber **108**.

8. An orifice **109** that provides a set flow rate, or rate of gas flow, with the input pressure provided by the second pressure regulator **105**.

9. A user interface mechanism or a sequencing mechanism **107** that allows the user to sequentially operate the two valves, first valve **103** and second valve **106**, to deliver a measured dose of gas. Specifically, the sequencing mechanism is coupled to the first valve **103** and the second valve **106**, wherein the sequencing mechanism **107** alternately opens and closes the first valve and second valve. The output of the second valve **106** is coupled to one end of the orifice **109** and the other end of the orifice **109** is coupled to the user **111** or patient.

10. A nosepiece for user **111** that seals against the user's nostril while gas is dispensed.

[0019] In Fig. 1, the device is configured so that the compressed gas cylinder **101** is coupled to the input of the first valve **103**, the output of the first valve **103** is coupled to the input on the first pressure regulator **104**, and the output of the first pressure regulator **104** is coupled to the input of the second pressure regulator **105** and to the measurement chamber **108**.

[0020] Further, as shown in Fig. 1, the output of the second pressure regulator **105** is coupled to the input of the second valve **106**, and the output of the second valve **106** is coupled to the orifice **109**. Orifice **109** is coupled to user **111**. The therapeutic gas passes from the measurement chamber **108** through the second pressure regulator **105** and orifice **109** to provide user **111** a constant volume of therapeutic gas.

[0021] The devices described herein may be configured as hand-held devices that deliver accurately controlled doses of carbon dioxide or other therapeutic gas into a user's nasal passages (to contact the nasal surface, nasal membrane, nasal mucosa, etc.) for medical purposes. The devices generally deliver multiple doses from a single pressurized vessel of carbon dioxide or other therapeutic gas, and each dose may be delivered at a fixed flow rate.

[0022] The size of the doses must generally remain relatively constant when operated over a temperature range of about 10-40°C. Because the critical temperature of carbon dioxide is approximately 31°C (i.e., within the device operating range), the state and pressure inside the cylinder is unknown. As a result, delivering controlled doses of gas from the vessel over this temperature range may be challenging. The physical state of the CO_2 in

the vessel can be saturated liquid, super-critical fluid or pressurized gas. The corresponding cylinder pressure can range from ~ 600 psi to ~2000 psi depending on the temperature and quantity of carbon dioxide in the cylinder. See Appendix B.

[0023] In some variations, to withdraw a dose of carbon dioxide or other therapeutic gas from a vessel of unknown state, the gas may pass through a pressure regulator and fill a volumetric or measurement chamber at a controlled pressure of approximately 200 psi. This technique of filling a volumetric chamber to a controlled pressure may allow the device to withdraw accurate, repeatable doses of gas from the vessel. To deliver the dose to the patient, the gas may be released from the measurement chamber, and passed through a second pressure regulator (reducing the pressure to approximately 1 atmosphere), and then passed through a 0.005" (0.013 cm) diameter orifice and into the nosepiece. The orifice provides a constant 8 psi pressure drop and generates a relatively constant flow rate of gas of approximately 0.5 standard liters per minute.

[0024] Fig. 1 shows a schematic representation of the dose measurement and delivery system that comprise an exemplary gas dispenser. The sequencing mechanism **107** controls the valve action and timing, and may take a variety of forms. The sequencing mechanism **107** may be based on strictly mechanical elements, or may employ microprocessor and electrical actuators to control the valves. That is, the sequencing mechanism **107** may be either a mechanical or an electronic apparatus.

[0025] In Fig. 1, the exemplary sequence of events for measuring and delivering a dose are as follows:

1. In the default, or "Ready" state, first valve **103** is closed and second valve **106** is open. First valve prevents the therapeutic gas from exiting the compressed gas cylinder **101**. Keeping second valve **106** open prevents pressure from building in the measurement chamber **108** due to leakage through first valve **103**.

2. Second valve **106** is closed

3. First valve **103** is opened, allowing the therapeutic gas to flow through filter **102** to the first pressure regulator **104**. The therapeutic gas flows through the first pressure regulator **104**, filling up the measurement chamber **108** until the designated chamber pressure is reached, at which point the first pressure regulator **104** stops the flow of the therapeutic gas.

4. First valve **103** is closed.

5. Second valve **106** is opened, allowing the therapeutic gas to flow from the measurement chamber **108** through the second pressure regulator **105** and through orifice **109**. The second pressure regulator **105** supplies a relatively constant pressure to the orifice **109**, which results in a constant flow of the therapeutic gas leaving the orifice **109** and being delivered to user **111**.

6. Once the measurement chamber **108** is empty, the system is once again in the default "Ready" state.

[0026] Hence, the therapeutic gas passes from the compressed gas cylinder**101** through the first pressure regulator **104** to the measurement chamber **108**, and then the therapeutic gas passes from the measurement chamber **108** through the second pressure regulator **105** to provide the user **111** or patient a constant volume of therapeutic gas.

[0027] In practical implementations of the device, various components, as illustrated in Fig. 1 may be combined. For example, the functions of the valve and pressure regulators may be integrated into a single unit.

[0028] The overall device, e.g., a handheld device, may also include mechanisms to attach the compressed gas cylinder **101**, to pierce the seal on the compressed gas cylinder **101**, to sequence the operation of the valves in a user-friendly manner, and count the number of doses dispensed from the compressed gas cylinder **101**. In addition, the device may include a nosepiece that seals against the user's nostril while a dose is dispensed.

[0029] Fig. 2 illustrates the flow rate performance an exemplary therapeutic gas dispenser. As shown, the flow rate performance is relatively constant for fill levels of the

compressed gas cylinder **101** from a fill level of 100% to approximately 10% fill level. Further, the performance is relatively constant over temperatures from 10° C to 40° C.

[0030] Fig. 3 illustrates details of one variation of the therapeutic gas dispenser, e.g., a hand-held dispenser. Shown in Fig. 3 are the cylinder attachment and pierce mechanism **301**, the nosepiece **302**, the secondary pressure regulator **303**, the primary pressure regulator **304**, and the measurement chamber **305**.

[0031] Fig. 4 illustrates further details of the dispenser device shown in Fig. 3. Shown in Fig. 4 are the following:

1. A standard-sized pressure vessel filled with liquid or super-critical carbon dioxide (**401**). Multiple doses of carbon dioxide are dispensed from this vessel. The vessel has a metallic seal that remains intact until the user activates the device.

2. A mechanism to attach and seal the cylinder to the device. This mechanism may consist of a threaded port with a face seal that mates against the top of the cylinder (**402**).

3. A mechanism for piercing the pressure vessel seal. The mechanism may consist of a spring-loaded mass (**404**) that, when released, drives a pin (**403**) into the seal. The spring may be a cylindrical coiled spring (**405**) (as shown in the drawings) or a tapered spring. The tapered spring would be designed to compress flat to reduce the size of the piercing assembly. A clip or pull-tab (**406**) may secure the assembly until the device is activated.

4. A filter (**407**) that prevents particles from passing from the cylinder into the device. The filter may consist of a sintered stainless steel frit or sintered plastic. The filter may prevent particles from the pierce pin or the ruptured seal from travelling into the device. The filter also slows the flow of carbon dioxide into the device and creates a significant pressure drop. This pressure drop decreases the chances that liquid or solid carbon dioxide may travel into the device.

5. A "primary" pressure regulator that may reduce the pressure of the carbon dioxide to a set value after it leaves the pressure vessel. In Fig. 4, the primary regulator consists of a spring-loaded piston (**408**, **409**) regulator; alternatively, a number of simple regulator configurations may be used. Examples of applicable pressure regulator configurations are described in Appendix A.

6. A volumetric chamber or measurement chamber (**410**) may be used to withdraw each dose from the vessel. It is filled with carbon dioxide gas at a pressure set by the primary pressure regulator.

7. A "secondary" pressure regulator that reduces the pressure of the carbon dioxide to a set value as it exits the measurement chamber (**410**). In Fig. 4, the secondary regulator consists of a spring-loaded piston (**411**, **412**) regulator; alternatively, a number of simple regulator configurations may be used. Examples of applicable pressure regulator configurations are described in Appendix A.

8. An orifice that provides a set flow rate with the input pressure provided by the secondary regulator.

9. A user interface mechanism that allows the user to sequentially operate the two regulators to deliver a measured dose of carbon dioxide gas.

10. A nosepiece (**413**) that seals against the user's nostril while carbon dioxide is dispensed.

Appendix A – Pressure Regulator

[0032] As previously stated, the devices described here include pressure regulators and a sequencing mechanism that controls valves associated with the pressure regulators. The described devices configure and functionally implement the pressure regulators in a manner not previously described. Various pressure regulator designs may be employed. This section describes the basic operation of pressure regulators that may be suitable in the therapeutic gas dispensers described herein.

[0033] Fig. 5 illustrates a number of commonly used "piston regulator" layouts along with the formulas used to predict their behavior. In all configurations, the output pressure P_{out} is dependent on the two areas A_1 and A_2, the input pressure P_{in}, and the spring force acting on the piston when the valve closes. In an ideal regulator, the ratio of the two areas A_2/A_1 would be zero. In this case, the output pressure Pout is only dependent on the area A1 and the spring force. In other words, the output pressure is independent of the input pressure.

[0034] Besides the mechanical differences, the main difference between layouts 1 and 2a/b is their response to changes in input pressure. In layout 1, the output pressure increases with increased input pressure. In layout 2a/b, the output pressure decreases with increased input pressure.

[0035] In this application, the response characteristics of layout 1 may be preferable to layout 2. Since it is desirable for the measurement chamber to fill with a repeatable mass of carbon dioxide or other therapeutic gas over the expected range of operating temperatures, it is preferable for the measurement chamber pressure to be slightly higher at higher temperatures. Since the input pressure increase at higher temperatures, it may be beneficial to use layout 1. Of course, the ideal regulator output pressure would be constant at all pressures and temperatures.

[0036] In addition to the piston regulators illustrated above, the devices described here may include analogous regulators that use diaphragms instead of pistons. This concept is illustrated in Fig. 6.

Appendix B – Phase Behavior of Carbon Dioxide

[0037] One of the important challenges that the devices described here address is the unknown state of the carbon dioxide in the pressure vessel. Over the operating range of 10-40°C, the pressure vessel may contain liquid carbon dioxide and saturated vapor, supercritical carbon dioxide, or carbon dioxide gas. The state depends on the temperature and the amount of carbon dioxide in the vessel. The pressure inside the vessel can range from

approximately 600 psi to over 2000psi depending on the temperature and the amount of carbon dioxide in the vessel.

[0038] Fig. 7 shows the phase diagram for carbon dioxide. The dotted lines represent the range of temperatures and pressures that may be present in the pressure vessel. The "critical" temperature for carbon dioxide is approximately 31°C. Liquid carbon dioxide cannot exist above this temperature.

CLAIMS

1. A device for dispensing a therapeutic gas to a patient comprising:

a compressed gas cylinder,

a first valve and a second valve,

a first pressure regulator and a second pressure regulator,

a measurement chamber that has a defined volume of therapeutic gas at a predetermined pressure set by the first pressure regulator, and

a sequencing mechanism that is coupled to the first valve and the second valve, wherein the sequence mechanism alternately opens and closes the first valve and second valve,

wherein the compressed gas cylinder is coupled to input of the first valve, and output of the first valve is coupled to input on the first pressure regulator, and output of the first pressure regulator is coupled to input of the second pressure regulator and to the measurement chamber,

wherein output of the second pressure regulator is coupled to input of the second valve and output of the second valve is coupled to the patient,

wherein the therapeutic gas passes from the compressed gas cylinder through the first pressure regulator to the measurement chamber, then the therapeutic gas passes from the measurement chamber through the second pressure regulator to provide the patient a constant volume of therapeutic gas.

2. The device as in claim 1, further comprising an orifice to control rate of gas flow, wherein the output of the second valve is coupled to one end of the orifice and another end of the orifice is coupled to the patient.

3. The device as in claim 1, wherein the sequence mechanism is either a mechanical or an electronic apparatus.

4. The device as in claim 1, wherein the therapeutic gas is carbon dioxide.

5. The device as in claim 1, wherein the measurement chamber stores a volume of therapeutic gas at a controlled pressure of approximately 200 psi.

6. The device as in claim 1, wherein the patient receives a constant flow rate of gas of approximately 0.5 standard liters per minute.

7. The device as in claim 1, wherein the patient receives the therapeutic gas at a controlled pressure of approximately 1 atmosphere.

8. The device as in claim 1, wherein the device is utilized in a hand-held dispenser.

9. A method for delivering intranasally a therapeutic gas to a patient comprising the steps of:

obtaining the device according to claim 1,

activating the sequence mechanism to open the first valve and close the second valve to allow the therapeutic gas to flow from the compressed gas cylinder to the measurement chamber,

activating the sequence mechanism to close the first valve and open the second valve to allow the therapeutic gas to flow from the measurement chamber to the patient,

wherein the patient receives the therapeutic gas at a constant flow rate and pressure.