DRUG DELIVERY DEVICE AND METHOD

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to drug delivery devices and, in particular, it concerns a drug delivery device and corresponding methods which employ a pressurized reservoir of liquid medicament with controlled release via a flow restriction and multiple valves.

Low-dosage infusion pumps, both external and implantable, have been developed to the point of commercial and medical acceptance. For certain applications, a simple "constant flow" device is sufficient. In many cases, however, where patients require adjustments in the dosage as a function of time, constant flow pumps are inadequate. A typical example is diabetes where the quantity of medication, such as insulin, to be infused varies due to requirements of the patient. Fluctuations can occur on a daily basis or more randomly as a function of the ingestion of food. Consequently, to address the shortcomings of constant flow devices and obtain significant flexibility in dosage rates, various "implantable programmable" pumps have been developed. In the definition of system requirements dealing with such implantable programmable pumps, a device which will provide programmable bolus and basal flow rates over a wide dynamic range is a standing system requirement. This requirement can be set forth in a practical sense by reference to the treatment of diabetes. It is known that the amount of medication, typically insulin, to be infused per unit of time, should be adjusted at certain time intervals. A patient's requirements may fluctuate either at set, known rates or may vary abnormally, for example, by the ingestion of food or by other transitory conditions. Those conditions will call for the administration of a bolus dose of infusate. In the daily administration of insulin, however, the patient may require a basal dose that is supplanted by bolus doses at, for example, meal times. The difference in flow rates between basal and bolus doses may be quite large, in the orders of several times. Thus, a device to achieve proper flow rates over the spectrum of desired rates must have the ability to continuously infuse, at very low flow rates, yet provide, periodically, a substantially increased flow rate. Thus, the design criteria can be summarized as requiring, in the first instance, the ability for

continuous basal drug delivery which is adjustable to varying choices of flow rate, including the ability to deliver a bolus dose at relatively high flow rates.

The requirements of programmability, wide range of flow rates, and failsafe operation greatly complicate the design of programmable drug delivery devices. Secondary issues such as power consumption, overall system life and economic viability limit the feasibility of many of the theoretical solutions that have been proposed to-date.

In an attempt to ensure failsafe operation, many programmable drug delivery devices employ a negative-pressure storage chamber, effectively precluding the possibility of drug leakage in the case of device malfunction. Examples of such devices, referred to as "negative pressure pumps", may be found in U.S. Patents Nos. 4,482,346 and 4,486,190. Both of these prior art devices are solenoid activated negative pressure pumps. A diaphragm storage chamber maintains the drug to be infused in a chamber having a diaphragm which separates the drug from propellant, normally freon, maintained at negative pressure. A solenoid is activated driving an armature and a bellows pumping element. This displacement of the armature opens a check valve which draws drug from the storage chamber into a downstream pumping chamber. A restriction will prevent backflow in the outlet during this short period. When the pump chamber is full, the check valve closes and the solenoid is then de-energized. A spring force typically displaces the bellows into the chamber pumping the drug through a restrictor and into the patient.

Negative pressure systems, while offering advantages of safety, suffer from major disadvantages. First, the negative pressure requirements require special precautions and equipment for filling and handling of the devices. Furthermore, since all of the drug must be positively displaced by a pump working against a pressure gradient, the devices have high power consumption, requiring bulky power sources and/or frequent battery replacement.

A second approach exemplified by U.S. Patents Nos. 4,299,220 and 4,447,224 employs a positive pressure storage chamber in combination with an accumulator pump. The positive pressure of the storage chamber eliminates the handling problems of negative pressure devices. Where sufficiently high pressure is

used to drive drug delivery without additional pumping, at least part of the power consumption is reduced, although many valve actuation elements are also consume a lot of power.

Despite the advantages of simplicity of implementation and energy efficiency, safety remains a major concern for positive pressure devices. Given the fact that drug chamber pressure is above body pressure, there remains a remote possibility for an overdose of drug should all valves in line with the output fail open at the same time. An improved degree of safety can be achieved in such systems by providing redundant valves. However, even with redundant valves, there remains some risk of multiple component failure which could result in overdosing. Depending upon the type of drug being administered, such overdosing could potentially be fatal.

A further problem associated with all types of programmable drug delivery devices is that of repeat usage. Throughout the field of medicine, there is a strong trend towards use of disposable components for infusion sets and the like. In the case of programmable drug delivery devices, the cost of the device is such that it is not presently feasible to produce single-use disposable devices. Furthermore, the subdivision of components between disposable "wet" components and reusable electronic and control components which is common in hospital infusion control systems such as the IVAC™ system is typically considered impractical here because of the extremely low flow rates and precision control required from such devices.

There is therefore a need for a programmable drug delivery device and corresponding methods of delivering drugs based upon a pressurized reservoir and which would reliably identify and appropriately address a range of malfunction conditions to avoid risk of drug overdosing. It would also be highly advantageous to provide a programmable drug delivery device and corresponding method facilitating subdivision of the device into reusable electronic and control components, and disposable components which come in contact with the drug. Finally, it would also be highly advantageous to provide a programmable drug delivery device which would have extremely low power consumption.

SUMMARY OF THE INVENTION

The present invention is a drug delivery device and corresponding method for metered delivery of a liquid medicament.

According to the teachings of the present invention there is provided, in a drug delivery device having a pressurized source of a liquid medicament delivering the liquid drug to an outlet via a flow path, the flow path including a flow restriction and first and second valves, a method for identifying the presence of a gas bubble in the flow path, the method comprising: (a) operating the first and second valves in such a manner as to ensure a pressure between the first and second valves significantly below a pressure of the pressurized source; (b) during a pressure accumulation period, maintaining the first valve open and the second valve closed; and (c) at the end of the pressure accumulation period, identifying the presence or absence of a gas bubble in the flow path based at least in part on a measurement of pressure between the first and second valves.

According to a further feature of the present invention, measurement of pressure between the first and second valves is performed by differential pressure measurement between the pressurized source and fluid in the flow path between the valves.

According to a further feature of the present invention, the first valve is closed at the end of the pressure accumulation period.

There is also provided according to the teachings of the present invention, in a drug delivery device having a pressurized source of a liquid drug delivering the liquid drug to an outlet via a flow path, the flow path including a flow restriction, a method for identifying the presence of a gas bubble in the flow path, the method comprising: (a) monitoring at least one parameter affected by a pressure drop across the flow restriction; and (b) when the at least one parameter satisfies a bubble-detection condition indicative of a reduced pressure drop across the flow restriction, indicating the presence of a gas bubble in the flow path.

According to a further feature of the present invention, the at least one parameter is a pressure measurement affected at least by a fluid pressure downstream relative to at least part of the flow restriction.

According to a further feature of the present invention, the pressure measurement is a differential pressure measurement indicative of a pressure differential between the pressurized source and a part of the flow path downstream relative to at least part of the flow restriction.

According to a further feature of the present invention, the bubble-detection condition is a value of the pressure measurement indicative of a fluid pressure above a threshold value downstream relative to at least part of the flow restriction.

According to a further feature of the present invention, the threshold value is defined relative to the pressure of the pressurized source.

According to a further feature of the present invention, bubble-detection condition is evaluated during flow of the liquid drug at a rate limited primarily by the flow restriction.

According to a further feature of the present invention, bubble-detection condition is evaluated using a pressure measurement indicative of a rate of pressure increase after closure of a valve downstream of the flow restriction.

According to a further feature of the present invention, the pressure measurement is taken after closure of a valve upstream of a pressure measurement location.

According to a further feature of the present invention, the at least one parameter is indicative of a rate of pressure increase in fluid pressure after closure of a valve downstream of the flow restriction.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings, wherein:

FIG. 1 is a schematic representation of a drug delivery device, constructed and operative according to the teachings of the present invention;

FIG. 2 is a flow chart illustrating the sequence of operation of the drug delivery device of Figure 1;

FIG. 3A is a graph of the drug delivery device of Figure 1 during normal flow with a first and second valves in an open state;

FIG. 3B is a graph similar to Figure 3A illustrating the variation in fluid pressure along the flow path in the presence of a partial occlusion of outlet flow;

FIG. 3C is a graph illustrating the variation in fluid pressure along the flow path during a valve-testing sequence with the first and second valves closed;

FIG. 3D is a graph illustrating the variation in fluid pressure along the flow path during a pressure test sequence under normal operating conditions with the first valve closed and the second valve open;

FIG. 3E is a graph similar to Figure 3D when the drug reservoir is near empty;

FIG. 3F is a graph similar to Figure 3D when the infusion set is disconnected;

FIG. 4 is an isometric view of a preferred implementation of the drug delivery device of Figure 1 including a body and a disposable cartridge;

FIG. 5 is a top view of the device of Figure 4;

FIG. 6 is a split-level cross-sectional view taken along the line VI-VI in Figure 5;

FIG. 7 is an enlarged view of the portion of Figure 6 designated VII;

FIG. 8 is an isometric view of a cam tightening element from Figure 7;

FIG. 9 is an enlarged isometric view of a piezoelectric actuator and mechanical amplifier shown in Figure 7;

FIG. 10 is an enlarged view of the portion of Figure 6 designated X;

FIG. 11 is a cross-sectional view taken along the line XI-XI in Figure 5;

FIG. 12 is an enlarged view of the region of Figure 11 designated XII;

FIG. 13 is an enlarged view of the region of Figure 6 designated XIV;

FIGS. 14A-14F are schematic views of the removable cartridge of Figure 4 together illustrating the flow path of a liquid medicament defined by the cartridge, wherein:

FIG. 14A is a side view of the removable cartridge showing its docking ports;

FIG. 14B is a cross-sectional view taken along line S-S of Figure 14A;

FIGS. 14C-14F are cross-sectional views taken through Figures 14A and 14B along the lines R-R, V-V, Q-Q and T-T, respectively;

FIG. 15 is a schematic representation of a drug delivery device similar to Figure 1 in which the first valve also provides a fluid flow restriction;

FIG. 16 is a schematic representation of a drug delivery device similar to Figure 1 modified by addition of an emergency pressure release mechanism suited to external devices;

FIG. 17 is a schematic representation of a drug delivery device similar to Figure 1 modified by addition of an emergency pressure release mechanism suited to both external and implantable devices;

FIG. 18 is a cross-sectional view taken through a pressurized reservoir of the present invention illustrating a preferred implementation of the emergency pressure release mechanism of Figure 17;

FIG. 19 is a flow chart corresponding to part of Figure 2 and illustrating a variant implementation of the present invention which performs an additional test for the presence of air bubbles; and

FIGS. 20A and 20B are graphs similar to FIG. 3C illustrating a pressure profile along the flow path of the device during the air-bubble test under normal operating conditions and in the presence of an air bubble, respectively.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is a drug delivery device and corresponding method for metered delivery of a liquid medicament.

The principles and operation of devices and methods according to the present invention may be better understood with reference to the drawings and the accompanying description.

Before addressing the details of the present invention, it should be noted that numerous features of the invention are believed to be of patentable significance alone, independent of the other features described herein. Examples of features believed to be patentable include but are not limited to: the apparatus and methods for detecting valve malfunction; the apparatus and method for detecting the presence of air bubbles within the flow path; the apparatus and methods for detecting full and/or partial occlusion; the apparatus and methods for detecting drug reservoir

content; the apparatus and methods for detecting disconnection of a drug delivery set; the low power consumption valve actuator arrangement; the apparatus and method for emergency reservoir pressure release; and the apparatus and method for employing reusable pressure sensors to measure fluid pressure within a disposable cartridge without compromising sterility of the cartridge contents. For the purpose of conciseness, the various features will be described herein in one or more preferred implementations which combine most, or all, of these features. It will be clear, however, to one ordinarily skilled in the art, that the various features may equally be implemented in a range of other contexts and may be used independently in otherwise conventional systems.

Referring now to the drawings, Figures 1-14F illustrate the structure and operation of a drug delivery device, generally designated **10**, constructed and operative according to the teachings of the present invention, for metered delivery of a liquid medicament to an outlet **12**, typically connected to an infusion set (not shown).

Referring specifically to the schematic representation of Figure 1, generally speaking, device **10** has a pressurized reservoir **14** configured for storing and supplying the liquid medicament at a pressure above atmospheric pressure, and a flow path in fluid communication with pressurized reservoir **14** and outlet **12**. The flow path includes a first valve **16**, a flow restriction **18** configured to limit fluid flow along the flow path, and a second valve **20**. Each of valves **16** and **20** assumes a normally-closed flow-blocking state and is selectively actuatable to an open state which permits fluid flow therethrough. When both the valves **16** and **20** are in the open state, the liquid medicament flows from the pressurized reservoir along the flow path to the outlet at a rate limited primarily by the flow restriction (corresponding to the fluid pressure distribution illustrated in Figure 3A).

Device **10** also has a pressure measurement arrangement **22** deployed to measure a differential fluid pressure between a first point **24** and a second point **26** along the flow path. At least part of flow restriction **18** is located within the flow path between pressure measurement points **24** and **26**, and one of the pressure measurement points **24** or **26** is positioned in the flow path between valves **16** and

20. In the preferred examples illustrated here, the first pressure measurement point **24** is located to measure the reservoir pressure prior to first valve **16** while the second measurement point **26** is between the valves distal to the flow restriction. It should be noted, however, that substantially equivalent functionality for all features described below can be achieved by positioning the first measurement point between the valves proximal to the flow restriction and the second measurement point distal to the second valve, all consequent required changes being self-explanatory to one ordinarily skilled in the art.

A controller **28** is electronically associated with pressure measurement arrangement **22** and first and second valves **16** and **20**, and is configured to selectively open the valves to deliver a defined quantity of the liquid medicament to the outlet. Preferably, controller **28** is configured to actuate pulsed opening of first and second valves **16**, **20** between the normally-closed state and the open state so that the fluid flow pulses provide a desired rate of delivery. The total valves-open time for each pulse is preferably calculated on the basis of an anticipated rate of flow determined from a measured fluid differential pressure during zero flow conditions between flow pulses. This calculation is based upon predetermined information about the fluid medicament viscosity, optionally supplemented by fluid temperature data obtained by a temperature sensor **30**. Alternatively, or additionally, the actual rate of flow can be monitored by measuring the pressure differential across restriction **18** during the pulse. This information can either be used to modify the valves-open time of the present pulse, or in calculating the duration of the subsequent pulse.

It will be immediately apparent that the present invention provides a particularly simple and energy efficient programmable drug delivery system in which a relatively high reservoir storage pressure provides all the energy required to deliver the drug to the subject. At the same time, the combination of two independently switchable valves **16**, **20** and pressure measurement arrangement **22** provides highly effective and near-immediate detection of a wide range of malfunction conditions, thereby ensuring extremely high levels of safety, as will now be detailed with reference to Figure 2.

Turning now to Figure 2, this illustrates a preferred sequence of operation of device **10**. First, at step **32**, controller **28** opens second valve **20** while leaving valve **16** closed, and pressure difference ΔP is measured (step **34**). In this zero-flow state, the pressure distribution along the flow path under normal conditions looks as illustrated in Figure 3D. Here, the first pressure measurement point **24** of pressure measurement system **22** is exposed to the current pressure of the reservoir, while the second pressure measurement point **26** is at outlet pressure which typically corresponds to the subcutaneous body-fluid pressure. As a result, ΔP is effectively a measurement of the reservoir pressure less a relatively small, relatively constant value.

This state is particularly useful for a number of device self-tests, as follows. Firstly, it is a particularly preferred feature of the invention that pressurized reservoir **12** includes an elastic pressurizing member, typically a spring-driven piston, such that a fluid pressure within the reservoir varies as a function of a volume of the liquid medicament currently stored. As a result, the measured pressure differential ΔP is indicative of the remaining volume of the liquid medicament in reservoir **12**. Thus, at step **36**, controller calculates from the measured pressure differential a volume of fluid remaining in the reservoir and, at step **38**, if the remaining volume is less than a minimum allowed volume value, controller **28** generates a low-remaining-volume indication. Figure 3E illustrates the fluid pressure distribution which occurs in this test state when the reservoir is near empty.

In addition to warning of low remaining volume, the remaining fluid quantity calculation is also preferably used to compare with the expected values based upon the quantity of fluid which has been delivered by the device. If a discrepancy between the expected quantity of fluid remaining and the quantity indicated by the measured pressure differential is determined to be significant according to some predefined criteria, a malfunction indication is generated.

In most preferred cases, maximum reservoir operating pressure is in the range of 4-10 atmospheres. Operating pressures in excess of about 4 atmospheres (i.e., about 3 atmospheres above ambient atmospheric pressure) are particularly

preferred due to the enhanced ability to dislodge blockages throughout the flow path due to the build-up of pressure behind the blockage. Since the outlet pressure is typically only very slightly above atmospheric pressure, the value of ΔP can typically be used as if it were a direct measurement of the reservoir pressure relative to atmospheric pressure.

Next, at step **40**, controller **28** checks for occlusion downstream of the device as evidenced by residual elevated pressure beyond the closed valve **16**. This would lead to a reduced reading of ΔP. This case can be distinguished from the case of depletion of the reservoir contents by a large discrepancy between the expected remaining drug volume (original volume less the amount delivered) and the remaining drug volume as calculated from the ΔP value. If at step **40** an unexpected drop in ΔP is detected, an alarm signal is generated (step **42**).

Then, at step **44**, controller **28** checks whether the infusion set or other output connection has become disconnected. This case can be identified by an increase in the measured value of ΔP as illustrated in Figure 3F. Since the variations in outlet pressure between the connected and disconnected states are small relative to the pressure difference between the reservoir and the output, reliable detection of disconnection requires comparison of the ΔP value with one or more previously measured valve. Most preferably, one or more most-recently sampled values of ΔP is compared with the statistical distribution of values of ΔP from previous cycles to determine whether there has been a statistically significant increase in pressure difference. If such an increase is detected, an alarm indication is generated at step **46**.

Then, at step **48**, the required valves-open flow pulse time is calculated and, at step **50**, first valve **16** is opened to allow commencement of a flow pulse. Optionally, if the pulse duration is sufficient to allow the pressure distribution to reach substantially steady state, monitoring of pressure difference ΔP during the pulse can be used to provide additional measurement of the actual flow rate and/or to provide early warning of partial occlusion. Specifically, Figure 3A shows a pressure distribution during normal steady-state flow conditions whereas Figure 3B

shows a similar distribution where a partial obstruction is present downstream. In the latter case, the measured value of ΔP drops significantly during the fluid flow pulse but returns to its full value when measured under zero flow conditions at step **34**. These measurements are used to calculate a corrected pulse length to ensure that the required dosage is delivered despite the reduced flow rate through the device. Additionally, the device may provide an early warning to the user or to a medical practitioner of possible impending occlusion so as to allow preventative correction before full occlusion occurs.

Parenthetically, it should be noted that, in many low dosage rate applications, the compliance of the device (i.e. capacity of the system components to expand to accommodate additional fluid volume) is sufficient to accommodate the entire volume of a single fluid flow pulse downstream of the flow restriction **18** even if the outlet is partially occluded. In this case, so long as the pulse volume passes the obstruction and the pressure downstream of the valves returns to normal outlet pressure in the period between successive pulses, the total volume of drug delivered in each pulse is substantially unaffected by the partial occlusion.

A further particularly preferred feature of the present invention is the performance of a valve function test, most preferably during each flow pulse cycle of the system. Conceptually, the valve function test is performed by closing both valves so as to trap a pressure differential across at least one of the valves and monitoring the pressure for a defined period to test whether leakage has occurred across the valve. Most preferably, by trapping a pressure intermediate between the reservoir pressure and the outlet pressure, it is possible to ensure a pressure differential across both valves simultaneously, thereby allowing testing of both valves for leakage simultaneously.

Referring again to Figure 2, the valve test is performed as follows. At the end of the designated flow pulse time, second valve **20** is closed first (step **52**) followed by closing of first valve **16** after a small time delay (step **54**). This fixes the pressure distribution as illustrated in Figure 3C with a pressure differential across both valves **16** and **20**. At step **56**, a first reading of the differential pressure ΔP_1 between points **24** and **26** is taken. After a given time delay, a second differential pressure reading

ΔP_2 is taken (step **58**) and the values are compared (step **60**). If the differential pressure has dropped ($\Delta P_2 < \Delta P_1$), this indicates that the pressure between the valves has increased due to leakage across first valve **16** and a corresponding alarm indication is generated (step **62**). If the differential pressure increases ($\Delta P_2 > \Delta P_1$), this indicates that the pressure between the valves has dropped due to leakage across second valve **20** and a corresponding alarm indication is generated (step **64**). If no malfunction is detected ($\Delta P_1 = \Delta P_2$), the flow pulse cycle terminates at **66** and the entire cycle repeats from step **32**.

An additional, or alternative, particularly preferred feature of the present invention is the provision of apparatus and method for detecting air bubbles in the flow path. By way of introduction, it will be noted that the use of a pressurized reservoir together with a flow restriction provides a particularly effective and convenient technique for identifying the presence of air bubbles. Specifically, during normal liquid-filled operation, the rate of flow along the flow path is limited primarily by the fluid impedance of the flow restriction. As a result, when valves are opened to allow fluid flow, a large proportion of the pressure differential between the pressurized source and the outlet is dropped across the flow restriction. When an air bubble reaches the flow restriction, the flow resistance is very much lower, resulting in an abrupt increase in volumetric flow rate through the flow restriction and a corresponding reduction in the pressure differential across the flow restriction. For relatively small bubbles, this increased volumetric flow rate serves to largely compensate for the presence of the air bubble so that the dosage delivered by the drug delivery device is not significantly changed. For larger bubbles, the change in flow rate and/or reduction in pressure differential are preferably used to identify the presence of a bubble and generate an alarm.

Thus, according to the teachings of the present invention, there is provided a method for identifying the presence of a gas bubble in the flow path of a drug delivery device including: (a) monitoring at least one parameter affected by a pressure drop across the flow restriction; and (b) when the at least one parameter

satisfies a bubble-detection condition indicative of a reduced pressure drop across the flow restriction, indicating the presence of a gas bubble in the flow path.

In its most general sense, this method can be implemented in a system differing significantly from that of Figure 1, for example, having no valves or only a single valve. The measured parameter may be an absolute or differential pressure measurement affected at least by a fluid pressure downstream relative to at least part of the flow restriction, or a rate of change of the pressure. In the case of a differential pressure measurement, the measurement is preferably indicative of a pressure differential between the pressurized source and a part of the flow path downstream relative to at least part of the flow restriction. The bubble-detection condition is then typically a value of the pressure measurement indicative of a fluid pressure above a threshold value downstream relative to at least part of the flow restriction, thereby indicating a reduced pressure drop across the flow restriction. The threshold value is preferably defined relative to the pressure of the pressurized source.

Depending upon the pressure measurement arrangement used, measurements may be taken during dynamic variation of the pressure, for example to derive a rate of change of pressure. According to one example, the rate of pressure increase may be monitored after closure of a valve downstream of the flow restriction. When an air bubble is present, this rate of pressure increase is much more rapid than when the liquid drug is present.

In another implementation, a pressure drop across the flow restriction may be monitored during flow of the liquid drug at a rate limited primarily by the flow restriction, i.e., during delivery of the drug. A sudden reduction in the pressure drop across the flow restriction is indicative of the presence of a bubble passing through the flow restriction.

Turning now to Figures 19 and 20, there is illustrated a particularly preferred implementation of the gas-bubble detection method of the present invention implemented in the context of, and in combination with, the other features of the device of Figure 1 or Figure 15. Specifically, Figure 19 shows steps **52**, **54**, **56** and **58** from Figure 2 with a modification to include a test for bubbles according to this

alternative or additional further aspect of the present invention. Prior to step **52**, both valves are open during delivery of a pulse of the liquid drug, and the pressure downstream of the flow restriction is relatively low. At step **52**, the second valve is closed and the pressure between the valves starts to rise at a rate limited by the flow restriction. At step **54** the first valve is closed so as to normally trap an intermediate pressure between the valves and at step **56** the differential pressure is measured. The time between closure of the second valve and the first valve is referred to as a "pressure accumulation period".

Figure 20A illustrates the fluid pressure profile along the flow path under normal operation at this step of the method. As seen clearly, the pressure between the valves V1 and V2 has a value intermediate between the reservoir pressure and the outlet pressure, and significantly below the reservoir pressure. Figure 20B shows a similar pressure profile for the case where a gas bubble is present. The low flow resistance posed by the flow restriction to the gas bubble results in a much more rapid process of pressure equalization across the flow restriction. As a result, after the same small time delay between closing the second valve and the first valve, the pressure caught between the valves is much closer to that of the reservoir, resulting in a significantly smaller measured $\Delta P1$.

Returning to Figure 19, this illustrates additional step **200** at which the pressure $\Delta P1$ between the valves is compared with an expected value, preferably defined relative to the reservoir pressure or the difference between the reservoir pressure and the outlet pressure. If $\Delta P1$ is less than a given threshold value, corresponding to an overly high pressure between the valves, the method proceeds to step **202** where an air bubble alarm is generated. Otherwise, the valve test procedure preferably proceeds with step **58** and the subsequent steps of Figure 2, as described above.

As mentioned above, the bubble detection method may optionally be implemented using real-time pressure measurement while liquid is flowing. It will be noted, however, that the particularly preferred configuration described herein performs the pressure measurements under zero flow conditions after fluid pressure has been trapped between the two closed valves. These zero flow conditions are

conducive to precise pressure measurement, and allow the use of measurement arrangements such as those of Figures 11 and 12 which may introduce a time lag into the measurements.

Turning now to Figures 4-14F, these illustrate a preferred implementation of device **10**. In addition to incorporating all of the structural features and functionality described above with reference to Figures 1-3F, this implementation also illustrates important features relating to subdivision of components between a reusable body and a disposable cartridge, and further illustrates power-saving actuator configurations, as will now be described.

Referring specifically to the overall views of Figures 4-6 and 11, these show device **10** made up of a body **70** and a removable cartridge **72**. Pressurized reservoir **12** and the entire flow path including valves **16** and **20** and flow restriction **18** are implemented as part of removable cartridge **72**, while the controller and it's associated electronic components are implemented as part of body **70**. This subdivision, which offers profound advantages with regard to the economic viability of the device, is non-trivial to implement due to the difficulty of achieving precise valve actuation and pressure measurement while all electronic components remain part of the reusable body **70**. Preferred solutions to these difficulties according to the teachings of the present invention will now be described.

Referring now to the valve structures shown, first and second valves **16** and **20** are here implemented as part of replaceable cartridge **72**. As seen in the enlarged view of Figure 10, each valve has an externally exposed actuator surface **74**, isolated from the fluid flow path through the valve, so that force applied to actuator surface **74** actuates the valve to assume its open state. In the implementation shown here, the valve has a head **76** integrally formed with a valve stem **78**. Valve head **76** has an elastomeric sealing ring **80** which seals against valve seat **82**. In the implementation shown here, valve stem **78** is supported and biased to its closed position by an elastomeric diaphragm **84** which also provides an external seal for the flow path through the valve. The external surface of diaphragm **84** at the rear of valve stem **78** provides the aforementioned actuator surface **74** such that force applied to surface **74** displaces the valve head away from its seat so as to open the

valve without exposing the fluid flow path to any external contamination. Actuator surface **74** is shown here engaged by an output surface of an actuator assembly **90** which is included in body **70**, to be described with reference to Figures 7-9.

Returning to Figure 6, there can be seen a pair of actuator assemblies **90** which are each deployed for engaging the actuator surface **74** of one of valves **16**, **20**. One of actuator assemblies **90** is shown enlarged in Figure 7. By way of introduction, piezoelectric actuators are known to have low power consumption and would therefore be ideal for battery-powered drug delivery devices such as that of the present invention. Nevertheless, they are not commonly used due to the very limited displacements which they typically provide. Furthermore, though it may be feasible to build a small-displacement high-precision valve to be actuated by a piezoelectric actuator, this becomes impractical where the valve is part of a low-cost disposable cartridge, and where the actuator and valve are located in separable components with insufficient precision of interrelation between them when they are brought together. To address these issues, the present invention combines a piezoelectric actuator with both a mechanical amplifier and an alignment adjustment mechanism to render use of power-efficient piezoelectric actuators feasible.

Actuator assembly **90** here includes a piezoelectric element **92**, typically implemented as a stack of piezoelectric layers as is known in the art, electrically actuatable to generate a first displacement. Specifically, in the example shown here, the piezoelectric element is configured to elongate in the direction viewed here as "up-down". Deployed around piezoelectric element **92** is a mechanical amplifier **94** which is configured to convert the displacement of the piezoelectric element into a much larger output displacement of an output arm **96** for displacing actuator surface **74** of the valve. In this case, the output displacement is substantially perpendicular to the piezoelectric element's direction of elongation. It should be appreciated that a wide range of known mechanical amplifiers may be used in this device, although the implementation as shown in Figures 7 and 9, which is based upon three integral hinges and skewing of the associated triangular geometry, is believed to be particularly advantageous for its compactness and large amplification ratio.

In addition to the enhanced range of displacement achieved by use of amplifier **94**, it is typically preferable to provide an alignment adjustment for bringing the actuator assembly **90** into close engagement with the valve actuation surfaces prior to operation of the device. In a preferred implementation illustrated here, eccentric cams **100**, detailed in Figure 8, are mounted at two positions along a rotary shaft **102** turned by an adjustment knob **104**. Each cam **100** is rotatably engaged with shaft **102** via an overriding clutch mechanism, typically based upon a spring-loaded ball **106**, which defines a predefined maximum tightening torque transferable from the shaft to the cam. As a result, rotation of adjustment knob **104** simultaneously rotates both cams **100** so as to push the actuator assemblies **90** into close engagement with their corresponding actuator surfaces **74**. Each actuator assembly is pushed forward until a predetermined mechanical resistance occurs at which point the overriding clutch prevents further transfer of torque to the cam. In this manner, a single rotating motion of adjustment knob **104** simultaneously achieves the appropriate extent of tightening motion independently for both actuator assemblies **90**.

Turning now to Figures 11 and 12, there is shown a preferred implementation of pressure measurement arrangement **22** which includes a differential pressure sensor **110** included within body **70**. Differential pressure sensor **110** is in fluid connection with two connectors, implemented here as hollow needles **112**. Removable cartridge **72** is formed with a pair of pressure sensing cells **114**, best seen in the enlarged view of Figure 12, each of which has a sensing volume **116** isolated from fluid in the flow path by a flexible membrane **118**. Each sensing cell **114** has a complementary connector for mating with the pressure sensor connectors. In the case of hollow needles **112**, the complementary connectors are preferably elastomeric seals **120** which can be pierced by needles **112**. When removable cartridge **72** is engaged with body **70**, each of the sensor connectors **112** mates with a corresponding complementary connector **120** such that the differential pressure sensor measures a differential pressure between liquid in the flow path at the first and second points without compromising sterility of the liquid medicament stored within the flow path defined by the disposable cartridge **72**.

In order to ensure effective transfer of fluid pressure along the conduits between needles **112** and sensor **110**, the pressure sensing cells **114**, the conduits and needles **112** are preferably pre-filled with a liquid. The liquid is retained within needles **112** even when exposed due to capillary forces.

It will be appreciated that various other forms of self-sealing connectors may be used to interface between differential pressure sensor **110** and pressure sensing cells **114**, as will be clear to one ordinarily skilled in the art. Nevertheless, the needle-based interface is believed to be particularly advantageous due to its small dead volume and its insensitivity to slight misalignments.

Turning now briefly to Figure 13, this shows a preferred implementation of a filling port **126** for the pressurized storage reservoir **12**. In the example shown here, port **126** is configured for filling by use of a standard needle and syringe. Although self-sealing ports for injection with a needle are well known *per se*, use of this filling technique for relatively high pressures is problematic due to the high occurrence of a quantity of drug spraying from the beveled end of the needle as it is withdrawn from the port. To address this problem, the preferred implementation of port **126** as shown here includes a primary elastomeric seal **130** and a secondary elastomeric layer **128** slightly spaced from the primary seal. The secondary layer **128** is preferably implemented as a disk which has a small range of free motion in the direction of insertion of a needle. During filling, a needle is advanced through both secondary layer **128** and primary seal **130** and the required volume of liquid medicament is injected into the reservoir. Then, as the needle is withdrawn, it first clears the primary seal where any spray is released between the two sealing elements. As a result, when the needle is further withdrawn from the secondary layer **128**, no further spraying of drug occurs. The ability of the disk to move axially within a cylindrical cavity is believed to cause slightly reduced pressure between the elements as the needle is withdrawn, thereby ensuring that any drug released between the elements is not at sufficient pressure to cause further spraying as the needle clears the secondary layer **128**.

Turning now to Figures 14A-14F, these illustrate the overall flow path from the pressurized reservoir **12** to outlet **14** as defined by disposable cartridge **72**.

Firstly, as shown in Figure 14E, two separate channels **132** extend from reservoir **12** to first valve **16** and lower pressure sensing cell **114**. In this context, it should be noted that the pressure within the beginning of the flow path through the valves is essentially the same as that within the reservoir itself and, for this reason, measurement of the reservoir pressure is considered herein within the definition of pressure measurement at a "point within the flow path". The outlet **134** of valve **16** is seen in Figure 14F as leading to the entrance to a capillary tube which provides flow restriction **18** (Figure 14B). At the top of the capillary tube, the flow path splits towards upper pressure sensing cell **114** and second valve **20** (Figure 14C). The output **136** of valve **20** returns to a vertical channel **138** (Figure 14D) which connects to output **14**.

Referring now briefly back to Figure 4, this also shows a preferred configuration for interlocking disposable cartridge **72** with body **70**. In the structure shown here, a sliding cover **160** is provided with a pair of inwardly projecting ridges **162** which engage corresponding slots **164** on cartridge **72** and a rail **166** on body **70**. The spring **168** which provides pressurization of reservoir **12** is here shown mounted to cover **160** so that it is brought into position to bias a piston **169** when the slide is assembled as shown in Figure 5. Once the body and cartridge are interlocked by sliding cover **160**, a retaining nut **170** is attached to the outlet projection **172** of the cartridge, thereby locking the cover in place. Nut **170** is also configured to function as a connector for attachment of the fluid delivery infusion set (not shown).

Turning now to Figure 15, it should be appreciated that the function of flow restriction **18** can optionally be performed by precise control of a valve. In this case, it is possible to combine the functions of first valve **16** and flow restriction **18** into a single continuously controllable or multi-state valve **16/18**. In all other respects, the structure and function of the device remain identical to that described above with reference to Figure 1.

Turning now to Figures 16-18, these illustrate an additional optional feature which can be used to advantage with the device of Figure 1. Specifically, although the double valve configuration and self-testing features of the present invention provide extremely effective safety precautions against overdosing, there remains at

least a theoretical possibility that failure to properly address an alarm condition and/or multiple component failures could result in release of excess medication due to the pressure gradient from the reservoir to the subject's body. To address this issue, certain implementations of the present invention feature a reservoir pressure release mechanism **150** associated with controller **28** and selectively actuatable to depressurize reservoir **12** so as to deactivate delivery of the liquid medicament to outlet **14**. Actuation of pressure release mechanism **150** is preferably triggered either by a persistent alarm condition which has continued for a predetermined time period without being remedied and/or immediately by predefined dangerous conditions such as the failure of the pressure sensor arrangement or the failure both valves to respond.

Figure 16 represents schematically an implementation of pressure release mechanism **150** for an external drug delivery device. In this case, a solenoid actuated needle **152** is selectively advanced to puncture an elastomeric seal **154** located between the reservoir and the first valve. When actuated, the entire pressurized contents of reservoir **12** are released via the open-ended needle, thereby canceling the pressure gradient from the reservoir to the subject's body and preventing continued delivery of the drug.

Figure 17 shows a similar system adapted so as to be suitable for both external and implantable devices. In this case, the region around the actuator spring of the reservoir is pre-sealed as a reduced-pressure cavity. In this case, pressure release mechanism **150** is implemented as a solenoid operated valve or frangible partition which, when actuated, allows fluid communication between the pressurized storage volume of the reservoir and the reduced pressure cavity in the spring volume. This allows the liquid medicament to bypass the spring-driven piston and fill the void behind the piston, thereby releasing the spring and canceling the pressure gradient from the reservoir to the subject's body.

Turning now to Figure 18, this shows a preferred implementation of the pressure release mechanism of Figure 17. In this case, the piston of the pressurized reservoir includes a diaphragm seal **156**. Incorporated into the stem of the piston is a piercing pin **158** associate with a solenoid actuator **160**. When the emergency

pressure release mechanism is actuated via electrical connections (not shown) by controller **28**, the solenoid actuator **160** draws piercing pin **158** downwards, thereby piercing the diaphragm and allowing escape of the pressurized liquid to a reduced pressure region in the volume of the cartridge above the piston.

It will be clear to one ordinarily skilled in the art that the pressure release mechanism such as is illustrated with reference to Figures 16-18 provides an additional back-up safety system applicable in other contexts which renders the use of pressurized reservoirs acceptable for a wide range of applications for which they would otherwise be ruled out for safety reasons.

It will be appreciated that the above descriptions are intended only to serve as examples, and that many other embodiments are possible within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. In a drug delivery device having a pressurized source of a liquid medicament delivering the liquid drug to an outlet via a flow path, the flow path including a flow restriction and first and second valves, a method for identifying the presence of a gas bubble in the flow path, the method comprising:

(a) operating the first and second valves in such a manner as to ensure a pressure between the first and second valves significantly below a pressure of the pressurized source;

(b) during a pressure accumulation period, maintaining the first valve open and the second valve closed; and

(c) at the end of the pressure accumulation period, identifying the presence or absence of a gas bubble in the flow path based at least in part on a measurement of pressure between the first and second valves.

2. The method of claim 1, wherein measurement of pressure between the first and second valves is performed by differential pressure measurement between the pressurized source and fluid in the flow path between the valves.

3. The method of claim 1, wherein the first valve is closed at the end of the pressure accumulation period.

4. In a drug delivery device having a pressurized source of a liquid drug delivering the liquid drug to an outlet via a flow path, the flow path including a flow restriction, a method for identifying the presence of a gas bubble in the flow path, the method comprising:

(a) monitoring at least one parameter affected by a pressure drop across the flow restriction; and

(b) when the at least one parameter satisfies a bubble-detection condition indicative of a reduced pressure drop across the flow restriction, indicating the presence of a gas bubble in the flow path.

5. The method of claim 4, wherein said at least one parameter is a pressure measurement affected at least by a fluid pressure downstream relative to at least part of the flow restriction.

6. The method of claim 5, wherein the pressure measurement is a differential pressure measurement indicative of a pressure differential between the pressurized source and a part of the flow path downstream relative to at least part of the flow restriction.

7. The method of claim 5, wherein the bubble-detection condition is a value of the pressure measurement indicative of a fluid pressure above a threshold value downstream relative to at least part of the flow restriction.

8. The method of claim 7, wherein the threshold value is defined relative to the pressure of the pressurized source.

9. The method of claim 5, wherein bubble-detection condition is evaluated during flow of the liquid drug at a rate limited primarily by the flow restriction.

10. The method of claim 5, wherein bubble-detection condition is evaluated using a pressure measurement indicative of a rate of pressure increase after closure of a valve downstream of the flow restriction.

11. The method of claim 10, wherein said pressure measurement is taken after closure of a valve upstream of a pressure measurement location.

12. The method of claim 4, wherein the at least one parameter is indicative of a rate of pressure increase in fluid pressure after closure of a valve downstream of the flow restriction.