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DESCRIPTION

[0001] This invention relates to improvements in or relating to methods of using a reagent cartridge and in particular, a reagent cartridge that can be used to dictate the flow rates of reagents upon the application of pressure.

[0002] A single flexible container contained within a rigid housing can be used to host fluids under high pressure. Fluids that are kept under high pressure are routinely found and used in everyday products such as aerosol cans and carbonated beverages. Additionally, sterile and fermenting products may provide a plurality of flexible containers within the rigid housing. However, the flow rates of the fluids in the containers are not routinely controlled to an accuracy of microlitres per minute or per hour in such products.

[0003] In the field of microfluidic systems, pressurizing fluids directly in rigid containers can provide a means for delivering the fluids and/or handling the flow of fluids to the microfluidic device. Microfluidic devices are prominent tools used in applied research and in commercial manufacturing processes. These microfluidic systems are routinely used to analyze, separate, isolate, or purify biological particles, such as DNA, RNA, carbohydrates and proteins.

[0004] The flow of fluids directly in rigid containers is typically carried out by directly pressurising the fluids with gases. These gases may dissolve into the fluids which may gas out at a later stage, or it may react (for example, oxidation) with the constituents of the fluids. In some instances, this may result in the unintentional contamination of the fluids.

[0005] Furthermore, the flow rates of pressurised fluids in single flexible containers are typically high for example, in the order of µL - 10 mL/s or higher and as a result, the flow rates are not easily controllable on a microliter per minute or hour level.

[0006] As a consequence, the proportion of fluids that flow from the flexible containers into the microfluidic device can vary substantially.

[0007] WO2015/195831 discloses a method of preparing reagents includes inserting a cartridge into an instrument. The cartridge includes a plurality of reagent enclosures disposed in a cavity of the cartridge and exposing a port to an exterior of the cartridge. Each reagent enclosure includes a reagent container including a reagent and an internal cavity defining a compressible volume, an opening defined through the reagent container to the internal cavity. The method further includes connecting a plurality of fluid ports to the openings of the plurality of reagent enclosures; applying a solution through the fluid ports to at least partially fill the plurality of reagent enclosures; and cycling a pressure of the cavity, whereby for each of the reagent enclosures, during increasing pressure, the solution enters the internal cavity of the reagent container, combines with the reagent, and compresses the compressible volume, and during decreasing pressure, the compressible volume decreases and the reagent is ejected through the opening.

[0008] US2011/180150 discloses a fluid delivery system which provides stable flow rates over a range of different flow rates and while multiple fluids are being concurrently delivered. The delivery system includes one or more reservoirs each containing a respective fluid to be transferred. The reservoirs are positioned within a secondary fluid selected such that the reservoirs and their contents float within the secondary fluid. One end of a flow conduit is submerged in each fluid to be transferred. A pressure differential is then induced in the flow conduit whereby fluid flow therein occurs.

[0009] US2009/209898 discloses a method for pumping or delivering fluids utilizing a flexible vessel subject to controlled pressures within another pressure vessel. The pressure vessel can be sourced with positive and/or negative (e.g., vacuum) pressure.

[0010] WO2008/032030 discloses a sealed container which provides a reservoir of reagent, buffer solution or other liquid for a scientific laboratory or diagnostic instrument or medical device. The liquid in the sealed container is in a degassed state and the container is flexible so as to be at least partially collapsible, thereby to inhibit the aeration of the liquid remaining in the container after the latter has been opened and some of the liquid removed.

[0011] It is against this background that the invention has arisen.

[0012] According to the present invention there is provided a method for discharging fluids from a plurality of flexible reagent containers into a microfluidic device using a fluidic system, the fluidic system comprising a rigid housing, a single pressure source (18) configured to apply pressure to the interior of the rigid housing, a plurality of flexible reagent containers (14) contained within the housing, a microfluidic device (25) configured to analyse one or more fluids provided from the plurality of reagent containers and a plurality of channels (20) configured to transfer fluid from the plurality of reagent containers to the microfluidic device, wherein the ratio of resistances provided by a combination of the connection ports and the plurality of channels dictates the ratio of flow rates of the reagents and wherein each reagent container has a connection port through which a reagent can flow, in use, on the application of pressure from the single pressure source; and wherein a plurality of reagents contained within the plurality of flexible reagent containers are configured to be actuated simultaneously by the single pressure source; and wherein the plurality of channels is connected to the connection ports of the reagent containers using closed valves that open upon connection, characterised by the method comprising simultaneously actuating the plurality of reagent containers by the single pressure source.

[0013] The flexibility of the reagent containers is particularly advantageous because it may substantially expand or contract in order to increase or decrease its volume and capacity to hold the reagents. In some embodiments, the capacity of the reagent containers may be substantially equal, so that the proportions of one or more reagents in the containers are equal. Conversely, the capacity of the reagent containers may substantially differ, so that the proportions of one or more reagents in the containers are different.

[0014] Providing a plurality of flexible reagent containers within the housing can be advantageous as it provides a means for hosting a plurality of different reagents that can be actuated simultaneously by a single pressure source. In some embodiments, the reagent can be a fluid. The fluid can be either a liquid or a gas.

[0015] The cartridge reagent of the present invention may further comprise an actuator which is configured to control the flow of the plurality of reagents by modulating the pressure from the single pressure source. The use of a single pressure source is particularly advantageous because it allows for an identical actuation of the plurality of reagents which minimises fluctuations in the relative flow rates. In some embodiments, the actuator used for modulating the pressure from the single pressure source may be a pressure pump. In some embodiments, the actuator may be user controlled.

[0016] The reagent containers may be fluid impermeable. This can be particularly advantageous as it provides a barrier between the reagent containers and the rigid housing. Furthermore, if the fluid is a liquid, it may be degassed prior to being introduced into the container and then the fluid impermeable nature of the reagent containers ensures that no gases can contaminate the liquid reagents. Additionally, the fluid impermeable containers may prevent the reagents within the containers to flow into the interior of the rigid housing. It may also prevent the other fluids, such as an actuating fluid, within the rigid housing from entering into the reagent containers.

[0017] In some embodiments, the reagent cartridge may further comprise a tube for introducing additional actuating fluid into the housing. The actuating fluid can be liquid or gaseous for example, air, nitrogen or liquid waste from the reagent cartridge.

[0018] The rigid housing may be a single housing. Alternatively, the rigid housing may comprise a plurality of pneumatically or hydrostatically connected containers.

[0019] In the context of the present invention, there is provided a fluidic system comprising a cartridge according to the previous aspect of the invention, the system further comprising a microfluidic device configured to analyse one or more fluids provided from the plurality of reagent containers.

[0020] The fluidic system further comprises a plurality of connecting channels which may contain capillaries configured to transfer fluids from the plurality of reagent containers into the microfluidic device.

[0021] The hydrodynamic resistance of the channel network or capillaries contributes to the ratio of the flow rates of the reagents from the containers. The ratio of resistances provided by the channel network attached to the connection ports does dictate the ratio of flow rates of the reagents. For example, the resistances of the connection ports or the attached channel network may be used to restrict the flow rate of the reagents.

[0022] In some embodiments the network of hydrodynamic resistances controls the flow rates of each of the reagents simultaneously during operation. In some embodiments the simultaneous control of reagents occurs in the context of steady state operation.

[0023] The resistance of the connection port or resistances of channels in series with the ports may be dictated by at least one of the cross sectional area of the port or channel, the length of the port or channel, and the surface roughness of the connection channels. For example, the length may be between 1mm and 2500mm and the diameter between 0.001mm and 10mm. More particularly, the length may be between 10mm and 2000mm and the diameter between 0.005mm and 5mm.

[0024] The resistance of the connection ports may be substantially equal so that the flow rates of the reagents are substantially equal. In some embodiments, the resistance of the connection ports may differ so that the flow rates of the reagents are different.

[0025] In the context of the claimed invention, the capillaries are connected to the connection ports of the reagent containers using valves that open upon connection. The use of valves that open upon connection is to avoid spillage and/or contamination during transport, handling and disposal. In some embodiments the closed valves that opens upon connection, includes but not limited to, needle free valves, swable valves or Luer-activated valves. Needle free valves can be used to prevent needle-stick injuries, thereby enhancing a user's safety when connecting the channel network to the connection ports. In some embodiments, the channel network may be connected to the connection ports of the reagent containers using quick connect connectors and adapters such as Luer connectors, barbed connectors or push-in connectors. In another embodiment, the channel network may be connected to the connection ports of the reagent containers using threaded connectors.

[0026] The fluidic system may further comprise a sump for collecting waste fluid flowing out from the microfluidic device. In some embodiments, the fluidic system may further comprise a drain tube configured to feed waste fluid from the sump into the rigid housing to replace the volume of spent reagents from the reagent containers, thus maintaining the dead volume of the container.

[0027] Feeding the waste fluid from the sump into the rigid housing may be beneficial as it allows for compensation of a change in hydrostatic pressure upon the discharge of reagents from the flexible containers. This may be useful for maintaining a constant hydrostatic pressure within the interior of the rigid housing. Furthermore, feeding liquid waste from the sump into the rigid housing may be beneficial as it allows for the flexible containers to be permanently encapsulated in liquid, which further decreases permeability to gases.

[0028] Preferably, the microfluidic device is chip based.

[0029] The invention is defined by the appended claims and will now be further and more particularly described, by way of example only, and with reference to the accompanying drawings, in which:

Figure 1 provides an illustration of a reagent cartridge according to the present invention; and

Figure 2 provides a further embodiment of the reagent cartridge.

[0030] Referring to Figure 1 there is provided a reagent cartridge **10** comprising a rigid housing **12**, a plurality of flexible reagent containers **14** contained within the rigid housing **12**. Each reagent container is configured to hold between 1ml and 2500ml of fluid, for example 100ml. Each reagent container **14** has a connection port **16** through which a reagent can flow upon the application of pressure. The reagent may be a fluid such as a gas or a liquid. As an alternative, the reagent may be a suspension, emulsion or a mixture. The reagent may contain biological or chemical components such as DNA, proteins, carbohydrates and/or organic compounds thereof. The flexible reagent containers may be configured to host the same reagents. Alternatively, the reagent containers may be configured to host different reagents.

[0031] The rigid housing may further comprise a tube (not shown) for introducing additional actuating fluid into the interior of the housing. The actuating fluid can be liquid or gaseous for example, air, nitrogen or liquid waste from the reagent cartridge.

[0032] By using flexible reagent containers contained within the rigid housing, the reagent containers provide a fluid impermeable barrier. The barrier can be utilised to prevent the reagents mixing with liquids or gases, such as the actuating fluids, within the rigid housing. Additionally, the reagent containers may also provide a means to prevent the reagents entering or leaking out into the interior of the rigid housing. The reagent containers may be made from multilayer plastics. In one embodiment the reagent containers are made from multi-layered plastics with aluminised film or other barrier layers.

[0033] A single pressure source **18** is configured to apply pressure to the interior of the rigid housing. The single pressure source is a flexible container **18** as illustrated in Figure 1. The single pressure source may be a pump **13**, in particular a pressure pump or peristaltic pump. An actuator can be provided which is configured to control the flow of the plurality of reagents by modulating the pressure from the single pressure source **18**. In some embodiments, the actuator can be user-controlled, for instance with a syringe or an external flexible container in pneumatic or hydraulic connection with the interior of the rigid container.

[0034] The pressure generated from the single pressure source may be used for pressurising the actuating fluids contained within the interior of the rigid housing. The pressurised actuating fluids can in turn, compress the plurality of flexible reagent containers. This causes the simultaneous actuation of reagents contained within the plurality of reagent containers. As a result, the reagents may be discharged or flow from the reagent containers into a device such as a microfluidic device **25.** This configuration aids the operation of the device in a steady state operation where simultaneous rather than sequential dosing of reagents is required.

[0035] As illustrated in Figure 1, each flexible reagent containers is connected to a connection port **16.** The connection ports of the reagents containers further comprises a plurality of connecting channels or capillaries **20.** The resistances in the channel network **20** are used to provide a connection between the connection ports of the reagent containers with the microfluidic device. The microfluidic device can be chip based. The channel network **20** may be connected to the connection ports using quick-connection connectors or fittings such as Luer connectors. Alternatively or additionally, the channel network **20** may be connected to the connection ports of the reagent containers using normally closed valves that open upon connection.

[0036] The channel network **20** connected to the connection ports **16** is configured to allow the reagents to flow from the reagent containers into the microfluidic device **25.** The microfluidic device may be configured to analyse one or more fluids provided from the plurality of reagent containers.

[0037] Conversely, the channel network **20** connected to the connection ports **16** may be configured to allow the reagents to be transferred from the microfluidic device into the flexible reagent containers **14.**

[0038] Each arm of the channel network **20** that is connected to a port of the reagent container may comprise an internal resistance which can be configured to dictate the flow rates of the reagents. The resistances attached to the connection ports are dictated by at least one of the cross sectional area of the port, the length of the port, and the surface roughness of the channel network or the viscosity of the fluid.

[0039] The resistances of the channel network connected to the ports of the reagent container may be substantially equal so that the flow rates of the reagents are substantially equal. This may provide a continuous flow of reagents between the reagent containers and the microfluidic device. Alternatively, the resistances of the channel network attached to each port may be substantially different so that the flow rates of the reagents are different. In all of the above mentioned embodiments, the use of a single actuation source and the setting of the resistance values, whether matched or divergent, provides a high-precision control of the flow of all of the reagents into the microfluidic device.

[0040] Each channel or capillary has a hydrodynamic resistance which can contribute to the flow rates of the reagents. The hydrodynamic resistances of the channels or capillaries are dictated by the geometry of the capillaries such as the cross sectional area of the channel or capillary, the length of the channel or capillary, and the surface roughness of the channel or capillary.

[0041] The flow of the reagents between the reagent containers and the microfluidic device can be a laminar flow or it can be a turbulent flow. Furthermore, the flow rates of the reagents can be affected by the viscosity of the reagents.

[0042] Additionally, as illustrated in the embodiment shown in Figure 2, there may be provided a sump **30** for collecting waste fluid flowing out from the microfluidic device **25.** The sump **30** may be a hollow or a depressed surface in which the waste fluids are collected. A drain tube **32** connected to the sump **30** can be configured to transport the waste fluids from the sump into the interior of the rigid housing as actuating fluids.

[0043] Feeding waste fluids such as liquids into the rigid housing may allow for compensation in a change of hydrostatic pressure upon reagents flowing out of the reagent containers. Therefore, the actuating fluids can provide a constant hydrostatic pressure within the rigid housing, which may help to minimise drift of the flow rates of the reagents. Maintaining the hydrostatic pressure within the housing also aids the high precision control of flows of reagents into the microfluidic device

[0044] Furthermore, surrounding the flexible containers with liquid may further reduce their permeability to gases. Alternatively, the reagent containers may be permanently immersed in liquid by having a container with a large amount of head room and long, impermeable connectors that attach the reagent containers to the top of the cartridge, or by connecting the reagent containers at the side or bottom of the rigid container.

[0045] Moreover, the rigid housing may comprise a plurality of pneumatically or hydrostatically connected containers (not illustrated in the drawings) for storing the reagents. Each pneumatically or hydrostatically connected container may have a connection port. The application of pressure to the pneumatically or hydrostatically connected containers may permit the reagents to flow from the containers into a device such as a microfluidic device. The pneumatically or hydrostatically connected containers can be used as an addition to the flexible reagent containers.

[0046] It will further be appreciated by those skilled in the art that although the invention has been described by way of example with reference to several embodiments, it is not limited to the disclosed embodiments and that alternative embodiments could be constructed without departing from the scope of the invention as defined in the appended claims.

REFERENCES CITED IN THE DESCRIPTION

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Patentkrav

1. Fremgangsmåde til udledning af fluider fra et modul af fleksible reagensbeholdere ind i en mikrofluidanordning ved hjælp af et fluidsystem, hvilket fluidsystem omfatter:

et stift hus (12),

en enkelt trykkilde (18), der er udformet til at anvende et tryk mod det indre af det stive hus (12);

et modul af fleksible reagensbeholdere (14), der er indeholdt i huset (12);

en mikrofluidanordning (25), der er udformet til at analysere ét eller flere fluider tilvejebragt fra flerheden af reagensbeholdere (14); og

et modul af kanaler (20), der er udformet til at overføre fluid fra flerheden af reagensbeholdere til mikrofluidanordningen; hvor hver reagensbeholder (14) har en forbindelsesport (16), hvorigennem et reagens kan strømme, i anvendelse, ved anvendelse af tryk fra den enkelte trykkilde (18);

hvor forholdet mellem modstande tilvejebragt af en kombination af forbindelsesportene (16) og flerheden af kanaler (20) dikterer forholdet for reagensernes strømningshastigheder; og hvor et modul af reagenser indeholdt i flerheden af fleksible reagensbeholdere (14) er udformet til at blive aktiveret samtidigt af den enkelte trykkilde (18);

hvor fremgangsmåden omfatter samtidig aktivering af flerheden af reagensbeholdere (14) ved hjælp af den enkelte trykkilde (18), **kendetegnet ved, at** flerheden af kanaler (20) er forbundet med reagensbeholdernes (14) forbindelsesporte (16) ved hjælp af lukkede ventiler, der åbnes ved sammenkobling.

2. Fremgangsmåde ifølge krav 1, hvor fluidsystemet endvidere omfatter en aktuator, der er udformet til at styre reagensstrømmen ved modulering af trykket fra den enkelte trykkilde (18).

3. Fremgangsmåde ifølge krav 1 eller krav 2, hvor reagensbeholderne (14) er uigennemtrængelige for fluid.

4. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor kanalens og portnetværkets (20) modstande i alt væsentligt er ens, således at reagensernes strømningsrater i alt væsentligt er ens.

5. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor de normalt lukkede ventiler, der åbnes efter tilkobling, indbefatter nålefrie ventiler, ventiler med børste og Luer-aktiverede ventiler.

6. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor flerheden af kanaler (20) er forbundet med reagensbeholdernes (14) forbindelsesporte ved hjælp af hurtigforbindelsesforbindere eller adaptere, der indbefatter, men ikke er begrænset til, Luer-forbindere, forbindere med modhager eller indtrykningsforbindere.

7. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, der endvidere omfatter en sump (30) til opsamling af affaldsfluid, der strømmer ud af mikrofluidanordningen (25).

8. Fremgangsmåde ifølge krav 7, der endvidere omfatter et afløbsrør (32) udformet til at tilføre affaldsfluid fra sumpen (30) ind i det stive hus som et aktiveringsfluid.

9. Fremgangsmåde ifølge et hvilket som helst af de foregående krav, hvor mikrofluidanordningen (25) er chipbaseret.

DRAWINGS

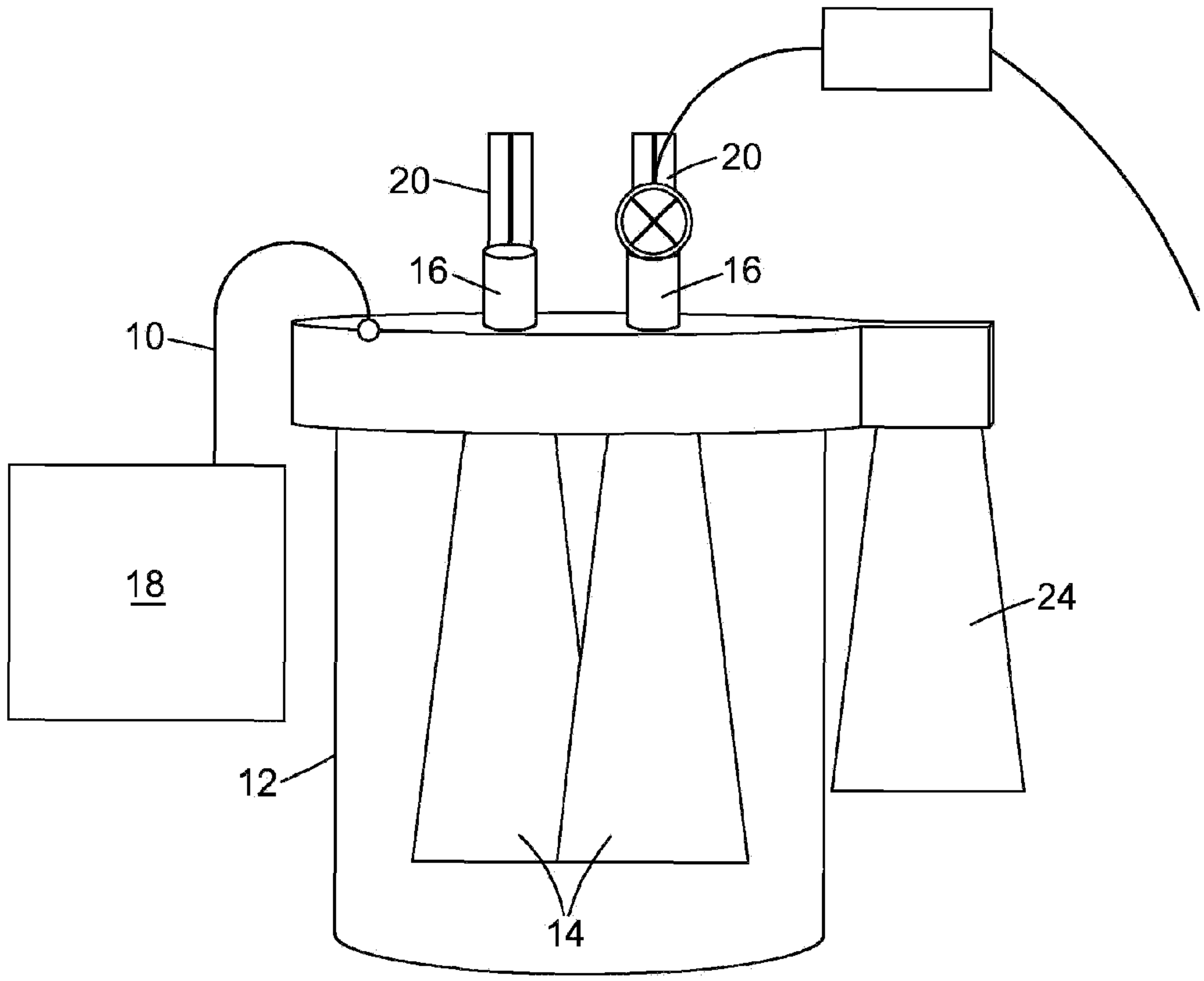

Fig. 1

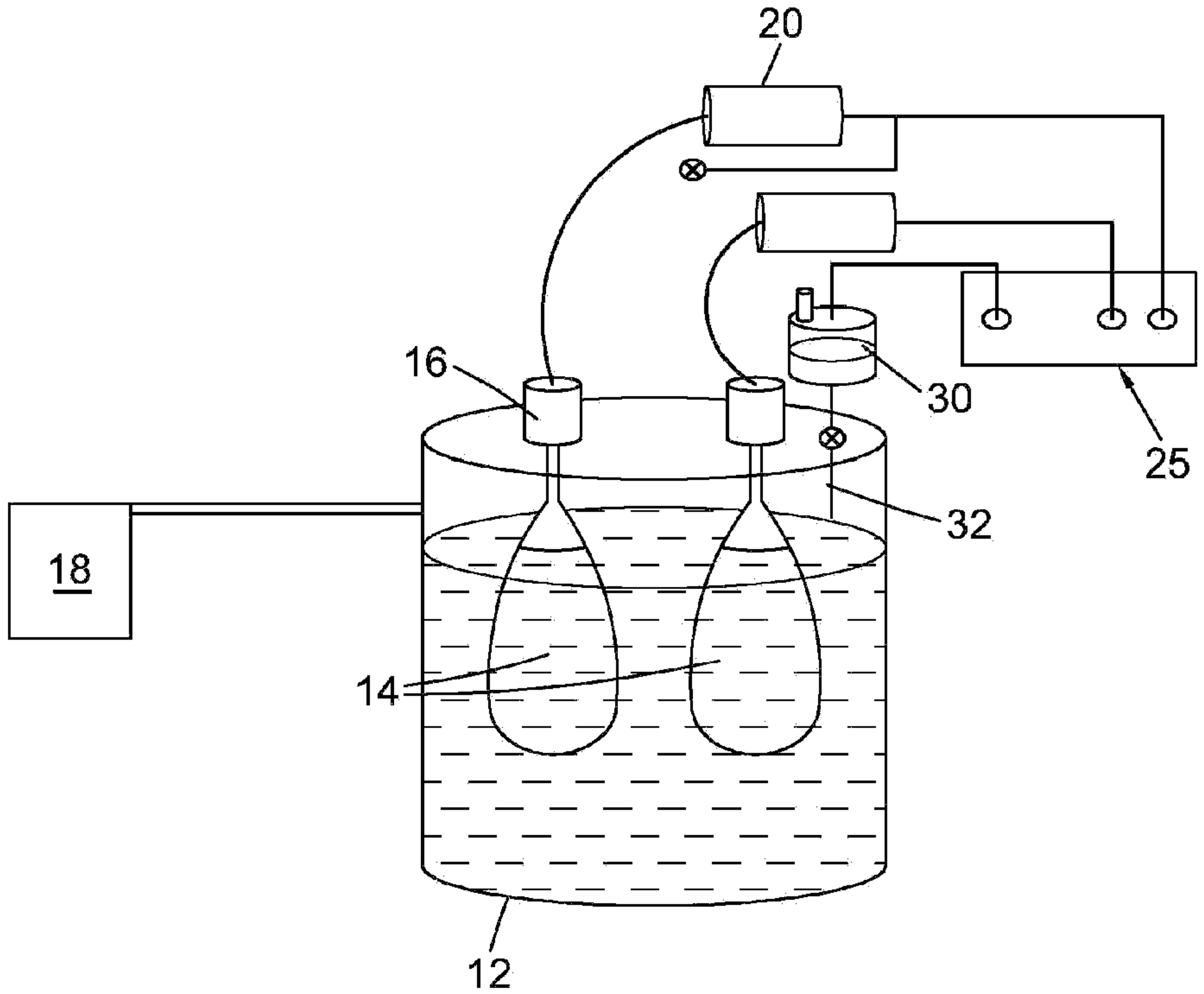

Fig. 2