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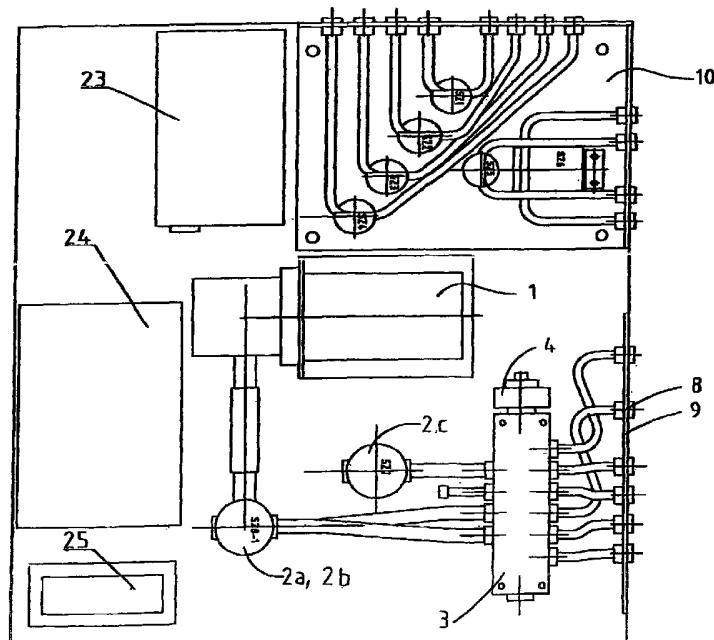
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(54) Title: REAGENT FEEDING APPARATUS



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(57) Abstract: The object of the invention is a reagent feeding apparatus comprising a reagent container, a liquid handling unit (container), and a control unit for controlling the process. The inventive apparatus is characterised by that it comprises a pneumatic unit (51), a fluid technology unit (10), reagent storage vessels, an electronic unit, and a control unit for controlling the process.

Reagent feeding apparatus

5 Technical field

The object of the invention is a reagent feeding apparatus comprising a reagent container and a liquid handling unit (container).

Background art

10 As it is widely known, processes of pharmaceutical, biological, chemical, biochemical, molecular biological etc. research are increasingly carried out using robotic systems. One of the major obstacles to full automation is that it is difficult to provide reagents in the quantities and with the stability that are required by robotic systems. Reagents for the process are usually provided
15 manually between process stages, using reagent containers, thereby causing a significant bottleneck in high-capacity robotic systems.

Disclosure of invention

20 The object of the present invention is eliminating the above mentioned drawback by providing a programmatically controlled apparatus that feeds the desired reagent automatically, complying with requirements set by the particular process into a reagent feed trough where it can be accessed by a robotic arm and can be transferred to its place of destination.

25 The inventive apparatus is based on the insight that in case automated liquid handling systems are operated continuously for a prolonged period of time, the automatic feeding of reagents in significantly increased numbers and quantities becomes possible, while, if required by the process, reagents can be continuously stirred (with emulsions and suspensions, maintaining homogeneity is an important practical goal). In addition, requirements set by
30 processes requiring special conditions can also be met, e.g. handling of

regulated temperature liquids is possible by means of an automated add-on heater-cooler unit, or the feeding of liquid substrates can be carried out by means of a steriley operable container and by modifying liquid paths of the apparatus (this option is included in the inventive apparatus). Additionally, for

5 handling oxidation-sensitive solutions inert gas can be used as a pneumatic medium without significant modification to the apparatus.

Although known art systems are capable of replenishing reagents, they cannot clean the reagent trough, are incapable of feeding more than one reagent or of mixing multiple reagents or withdrawing the extra reagent and

10 transfer it to a container. Reagents cannot be stored in inert gas atmosphere before being fed into the process, cannot be tempered while under storage, and cannot be mixed.

Known art solutions provide for the software-driven feeding of a single reagent only (e.g the TeMo option for RSP robots made by TECAN,

15 Switzerland). Existing solutions also include replenishers based on the "bird watering principle," but similarly to other known art systems they can feed a single reagent only, and, though sterilisation is possible, they are incapable of being controlled by the system control software.

The above mentioned aims of the invention are achieved by providing an

20 apparatus comprising a reagent container and a liquid handling unit (container), with the apparatus being characterised by that it comprises a pneumatic unit, a fluid technology unit, a reagent feed trough, a reagent storage vessel, an electronic unit and a control unit for controlling the process.

25 The pneumatic unit of a preferred embodiment of the inventive apparatus consists of a compressor, two two-way valves and a pressure relief valve (with said valves being connected to said compressor), a block-shaped distributor block, and connecting pipes, with the distributor block comprising serrated and tapered pipe connectors on the longer sides thereof; where the
30 serrated pipe connectors are connected to valves and where said distributor

block further comprises threaded bores on the shorter sides thereof, with said bores receiving a plug and a pressure gauge disposed at opposite shorter sides of said distributor block.

Another preferred embodiment of the inventive apparatus is characterised by

5 that the fluid technology unit thereof comprises valves disposed on a first support plate, first pipe connectors disposed on a second support plate, second pipe connectors disposed on a third support plate, and conduits; where said first pipe connectors are connected to the reagent feed trough, and where said conduits connect said first and second pipe connectors with

10 said valves; with the electronic unit of the apparatus comprising a power supply, a first circuit board containing the control electronics, a second circuit board containing the display electronics, and push buttons.

A further advantageous embodiment of the apparatus is characterised by that the reagent feed trough thereof comprises connection means for

15 establishing connections with a reagent storage vessel or vessels and with the control electronics, and also by that the reagent feed trough thereof further comprises four reagent inlet openings, a drain opening, sensor probes disposed in grooves formed in the side walls of the trough, and a motor, where said sensor probes detect the level of liquid in said trough, and

20 where said motor is applied for stirring the liquid contained in the trough, with the troughs of the apparatus being made of Teflon or POM (poly-oxy-methylene).

A preferred embodiment of the inventive apparatus comprises three troughs in a serially connected configuration.

25 Another preferred embodiment of the apparatus according to the invention is characterised by that the reagent storage vessel thereof comprises a Teflon adapter comprising elements that are connected to the principal air and liquid lines of the apparatus.

Brief description of drawings

A preferred embodiment of the apparatus according to the invention will now be described with reference to the attached drawings, where

Fig. 1 is a schematic view of the inventive apparatus,

5 Fig. 1a shows the front view of the control electronics panel of the apparatus according to Fig. 1,

Fig. 2 is a top plan view of the distributor block shown in Fig. 1,

Fig. 3 is a sectional view of the distributor block shown in Fig. 2,

Fig. 4 shows the top plan view of the fluid technology unit of the apparatus 10 shown in Fig. 1,

Fig. 5 shows the top plan view of the reagent feed trough of the apparatus shown in Fig. 1,

Fig. 6 is a side view of the reagent feed trough of the apparatus shown in Fig. 1,

15 Fig. 7 shows the longitudinal cross section of the reagent feed trough of the apparatus shown in Fig. 1,

Fig. 8 shows the adapter that is connected to the reagent storage vessel of the apparatus,

Fig. 9 is the process chart of the inventive apparatus,

20 Fig. 10 shows the functional diagram of the apparatus according to the invention, and

Fig. 11 shows the schematic diagram of an embodiment of the inventive apparatus that is suitable for sterile handling of liquids.

25 Best mode of carrying out the invention

The pneumatic unit of the inventive apparatus essentially consists of a compressor 1 mounted on a support element, two two-way valves 2a, 2b, a pressure relief valve 2c, and a distributor block 3. The two-way valves 2a, 2b, the pressure relief valve 2c, a pressure gauge 4, and fast connectors 8,

30 connected to air conduits leading to liquid storage vessels (not shown here)

that are mounted on the side of the apparatus, are all connected to the distributor block 3.

The distributor block 3 is a block-shaped element, comprising on its longer sides serrated pipe connectors 5 connected to valves 2a, 2b, and 2c, and 5 tapered pipe connectors 6 connected to the reagent storage vessels. A plug 7 is situated on one of the shorter sides of the distributor block 3 (see Fig. 2). Threaded bores 29, 22 are formed in the distributor block 3 for receiving the serrated and tapered pipe connectors 5, 6.

10 The plug 7 is also received in a threaded bore 31 of the distributor block 3, while the pressure gauge 4 is received in another threaded bore 34 machined into the wall of the distributor block opposite to the plug 7 (see Fig. 3).

15 Another important constituent part of the inventive apparatus is a fluid technology unit 10 that consists of valves 13a, 13b, 13c, 13d and 13e mounted on a support plate 12. The valves 13a, 13b, 13c, 13d, 13e are connected to the liquid storage vessels and to the reagent feed trough 40 (to be described later in this document) by means of pipe connectors 15 that are disposed on a support plate 18 that forms the back part of the cover of the apparatus. Valves 13a, 13b, 13c, and 13d are applied to control the feeding 20 of the four different reagents handled by the apparatus, while valve 13e is used for controlling the feeding of cleaning liquid. A further valve 14 is applied for removing used cleaning liquid and residue solution from the trough 40 to a waste storage vessel (the trough and the storage vessel are not shown in the drawings).

25 Valves 13e and 14 are mounted on a valve support element 20, and are connected to pipe connectors disposed on a support plate 17. The fluid technology unit is fixed to the base plate of the apparatus by means of fasteners placed in holes 19 situated in the four corners of the support plate 12 of the unit (see Fig. 4).

The apparatus further comprises an electronic unit that consists of a power supply 23, a circuit board 24 containing the control electronics, and a second circuit board 25 that is mounted on the inner side of the front panel of the apparatus and holds the display electronics and push buttons applied for operating the apparatus. The electronic unit is operated with 12 V DC provided by the power supply 24. The power supply 24 can be connected to a 220 V mains socket using a power cord that can be plugged into a socket (not shown here) situated on the back of the apparatus.

5

As it has already been mentioned, the second circuit board 25 is mounted on the front panel 26 of the apparatus, and comprises push buttons 27 and a display 28 (see Fig. 1a).

A very important part of the inventive apparatus is the reagent feed trough 40, which comprises means for connecting it to the liquid storage vessel and to the electronic unit.

10 15 The inside of the reagent feed trough 40 is preferably made of Teflon or POM. Due to advantageous physical and chemical properties of its constituent material, the trough 40 is resistant to aggressive chemical reagents and has reduced wettability, which makes cleaning easier and eliminates the danger of contamination when applying different reagents 20 after one another.

An arrangement of at most three troughs 40 can be applied in the inventive apparatus, with the troughs set up in a serial connection by means of connecting elements that ensure the liquid-tight fit of neighbouring troughs 40.

25 The trough 40 comprises four reagent inlet openings 34, an opening 35 for injecting cleaning liquid into the trough, and a drain opening 36 (see Fig. 5), with a pipe connector 41 screwed into each opening providing for connecting pipes to the trough 40 (Fig. 6).

30 The pipes or conduits run in grooves machined into the side walls of the trough 40, with the serial arrangement of the troughs ensuring that all

conduits can be passed out from the interior of the unit. Sensor probes 50 are disposed in grooves 37 formed in the two narrower sides of the trough 40. The probes 50 reach through the wall of the trough 40 as far as the inner space thereof, and provide for detecting the level of the liquid stored in the

5 trough 40. Thus, level monitoring in the trough 40 can be carried out by means of the sensor probes 50 that are designed to distinguish between level values of 0, 50, 100, and 110%. Connecting wires of the sensor probes 50 (soldered to the probes but not shown in the drawings) are lead to the bottom part of the trough in said outside groove 37 to pass out of the unit.

10 Sensor connecting wires are connected to the apparatus via a connector not shown here.

Fig. 7 shows the longitudinal cross section of the trough 40 which comprises a stirring motor 42 housed in a bore 38 in the bottom of the trough 40, with a magnet holder 43 and a stirring magnet 44 contained in said magnet holder

15 being attached to the motor shaft.

Stirring of the reagent is carried out by the magnet 44 that by means of magnetic interaction exerts torque on the motor holder 45 disposed in a bore that is located at the bottom of the inner cavity 40a of the reagent feed trough 40.

20 A groove 37a extends through the top and in the side of the trough 40 (Fig. 6), which, in case of a reagent overflow caused by the malfunction of the apparatus, directs the reagent towards the bottom, thereby preventing the contamination of the whole unit.

Fig. 8 shows the connecting adapter of the reagent storage vessel applied in

25 the apparatus according to the present invention. The plug of a known art borosilicate glass reagent storage vessel with G75 thread has been modified by adding a Teflon adapter 39, by means of which the vessel can be connected to the liquid line of the apparatus through an attached pipe connector 49a as well as to the air line thereof using a tapered connector 6.

30 By means of the tapered connector 6 air flows through the adapter 39 into

the vessel, while the liquid stored in the vessel gets into the liquid line of the apparatus through a plastic pipe 49, reaching down to the bottom of the vessel and pressed on pipe connector 49a.

In Fig. 9 the process chart of the inventive apparatus is shown, giving an 5 idea of the operation of the compressor 1, valves 2a, 2b and the distributor block 3 as well as the operation of valves 13a, 13b, 13c, 13d, 13e, 14 and the front panel 24.

10 The operation of the apparatus according to the invention will now be described in more detail.

The vacuum or overpressure generated by the compressor 1 is fed into the distributor block 3 corresponding to the setting of valves 2a, 2b. A signal is given by the pressure gauge 4 (attached to the distributor block 3) to the electronic unit, which controls the compressor 1 according to process 15 parameters set by the user. Depending on the desired direction of liquid flow, vacuum or overpressure is produced in the liquid storage vessels by means of pipes connected to the distributor block via fast connectors. If overpressure is produced in the vessels, the liquid contained therein is transferred through liquid lines to the reagent feed trough 40. In case stirring 20 is needed for the liquid fed into the trough 40, the solution can be stirred continuously by means of the magnetic stirrer built into the bottom of the trough 40. If it is required to take back residual reagent from the trough 40 after a stage of the process has been completed, vacuum is applied and the liquid is taken back into the storage vessel, reducing the liquid level in the 25 trough 40 to the height of the reagent inlet opening. Feeding of reagents and cleaning liquids is controlled by opening or shutting off valves of the liquid line of the apparatus. Valves 13a, 13b, 13c, 13d, 13e, and 14 are controlled by the electronic unit upon orders received from a software application.

The functional diagram of the first embodiment of the apparatus is shown in Fig. 10. Air is fed from the distributor block 3 of a pneumatic unit 51 into a liquid storage vessel 52 through an air conduit 53 connected to the distributor block and through the air inlet of a connector unit 57, while the liquid gets 5 into a reagent feed trough 40 through a liquid outlet connected to a liquid line 54 and through one of valves 13a-13d of the fluid technology unit 10, with the trough 40 being connected to an electronic unit by means of an electric wire 55.

According to this embodiment, valves 13a-13d are applied for controlling the 10 flow of the liquid.

In order to prevent different reagents from mixing, the reagent feed trough 40 can be filled up with cleaning liquid before switching to a new reagent. After 15 cleaning the used cleaning liquid is removed into the waste storage vessel. To increase cleaning efficiency, the cleaning liquid can be stirred using the magnetic stirrer means built into the bottom of the trough 40.

The apparatus can be used for preparing reagent mixtures on the spot, enabling the production of mixtures with the relative proportion of the four 20 reagents set arbitrarily. Also, small amounts of other reagents can be added to the mixture by injecting them externally into the trough 40. Homogeneity of prepared solutions is ensured by the application of the magnetic stirrer means.

When the apparatus is used for sterile liquid handling, the distributor block 3 is connected to valves 13a-13d instead of the liquid storage vessels. The liquid is pumped into the trough 40 by means of pressurized air that is fed 25 into the liquid storage vessel 52 through the valves and a sterile filter. Thus, the conduits, the storage vessels and the reagent feed trough 40 can be sterilised in a single run. The operation the suitable embodiment of the apparatus is shown in Fig. 11.

According to this embodiment, air is fed from the pneumatic unit 51 through 30 an air conduit 53 directly to the valves 13a-13d, so here the valves 13a-13d

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are applied for controlling the flow of pressurized air. After the valves 13a-13d, air passes through an air filter 56 and is fed into the storage vessel 52, whence liquid is pumped into the trough 40 through a liquid line 54.

5 The invention is not restricted to particular embodiments shown in the attached drawings. For instance, the inventive apparatus can be implemented in such a way that the pneumatic and fluid technology units form a single, common structural unit.

10 The configuration of this common unit should be obvious for those skilled in the art without any further tuition extending out of the scope of the present invention.

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Claims

1. A reagent feeding apparatus comprising a reagent container, a liquid handling unit (container), and a control unit for controlling the process, characterised by that it comprises a pneumatic unit (51), a fluid technology unit (10), a reagent storage vessel, an electronic unit and a control unit for controlling the process.
5
2. The apparatus according to Claim 1, characterised by that the pneumatic unit thereof consists of a compressor (1), two-way valves (2a, 2b), a pressure relief valve (2c), a distributor block (2) and connecting pipes, where said valves (2a, 2b, 2c) are connected to said compressor (1).
10
3. The apparatus according to Claim 2, characterised by that it comprises a block-shaped distributor block (3) comprising serrated and tapered pipe connectors (5, 6) on the longer side thereof, where the serrated pipe connectors (5) are connected to valves (2a, 2b, 2c) and the tapered pipe connectors (6) are connected to the reagent storage vessel, with said distributor block (3) further comprising threaded bores (31, 34) on the shorter sides thereof, where said bores receive a plug (7) and a pressure gauge (4) disposed at opposite shorter sides of said distributor block (3).
15
4. The apparatus according to any one of Claims 1-3, characterised by that the fluid technology unit (10) thereof comprises valves (13a, 13b, 13c, 13d, 13e, 14) disposed on a first support plate (12), first pipe connectors (15) disposed on a second support plate (18), second pipe connectors (16) disposed on a third support plate (17), and conduits, where said first pipe connectors (15) are connected to the reagent feed trough (40), and where said conduits connect said first and second pipe connectors (15, 16) with said valves (13a, 13b, 13c, 13d, 20
25
30
30

5. The apparatus according to any one of Claims 1-4, characterised by that the electronic unit thereof comprises a power supply (23), a first circuit board (24) comprising the control electronics, a second circuit board (25) comprising the display electronics, and push buttons (27).
- 5 6. The apparatus according to Claim 5, characterised by that the electronic unit thereof is implemented in such a way that it can be connected to an external computer system.
- 10 7. The apparatus according to any of Claims 1-6, characterised by that the reagent feed trough (40) thereof comprises connection means for establishing connections with reagent storage vessel or vessels and with the control electronics.
- 15 8. The apparatus according to any of Claims 1-7, characterised by that the reagent feed trough (40) thereof comprises four reagent inlet openings (34), a drain opening (36), sensor probes (50) disposed in grooves (37) formed in the side walls of the trough (40) and a motor (42), said sensor probes detecting the liquid level in said trough (40), and where said motor (42) is applied for stirring the liquid contained in the trough (40).
- 20 9. The apparatus according to Claim 8, characterised by that it comprises a magnetic motor (42),
10. The apparatus according to any of Claims 1-9, characterised by that the troughs (40) thereof are made of Teflon.
11. The apparatus according to any one of Claims 1-9, characterised by that the troughs (40) thereof are made of POM, poly-oxy-methylene.
- 25 12. The apparatus according to any of Claims 1-11, characterised by that it comprises three troughs (40) in a serially connected configuration.
13. The apparatus according to any of Claims 1-12, characterised by that the reagent storage vessel thereof contains a Teflon adapter (39) comprising elements (6, 49a) connected to the principal air and liquid lines of the apparatus.

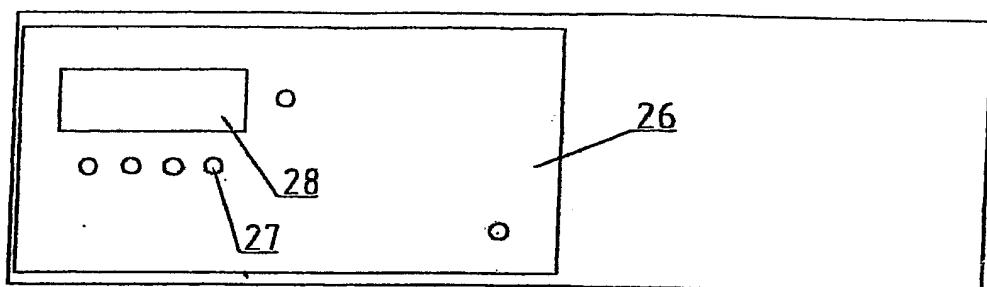


Fig. 1a

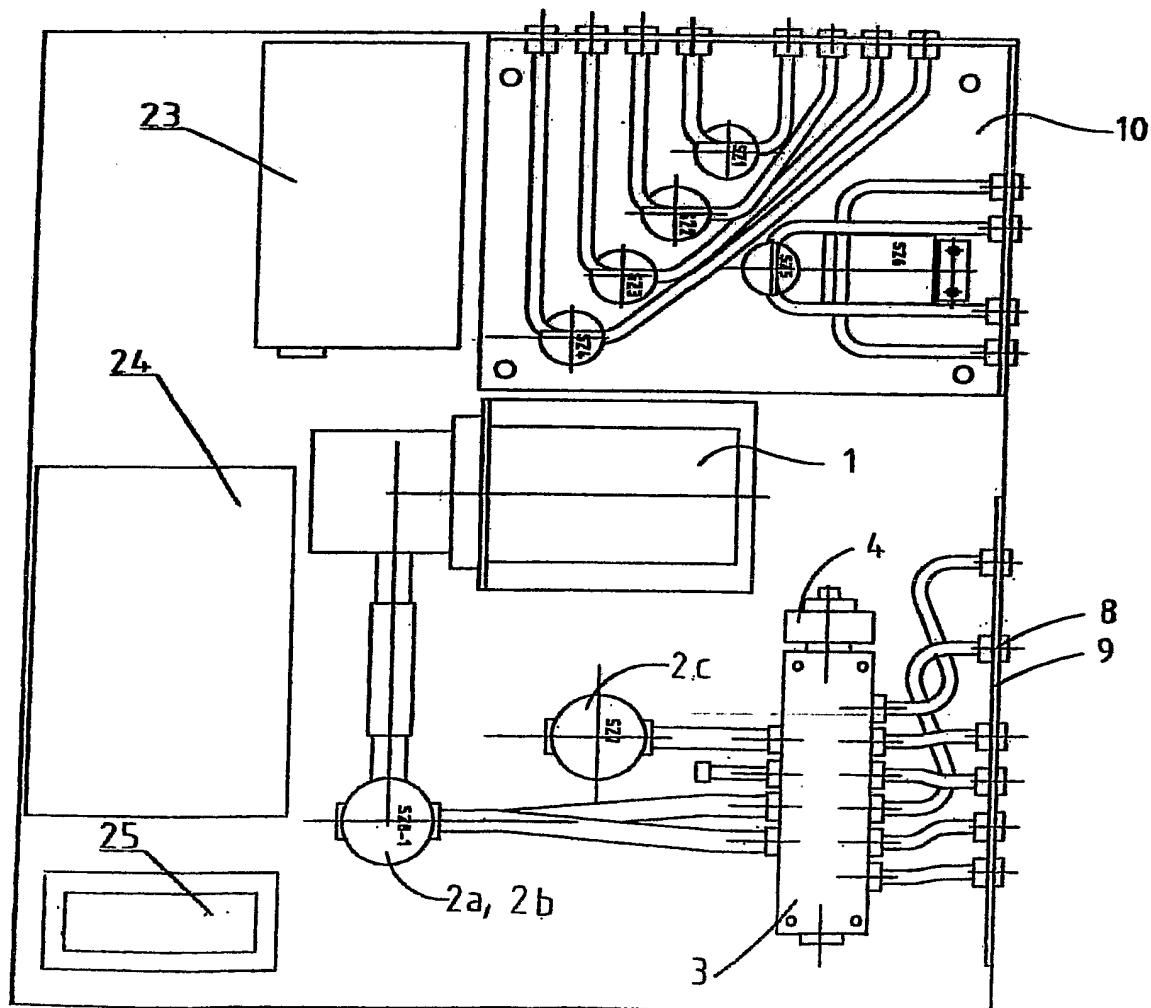


Fig. 1.

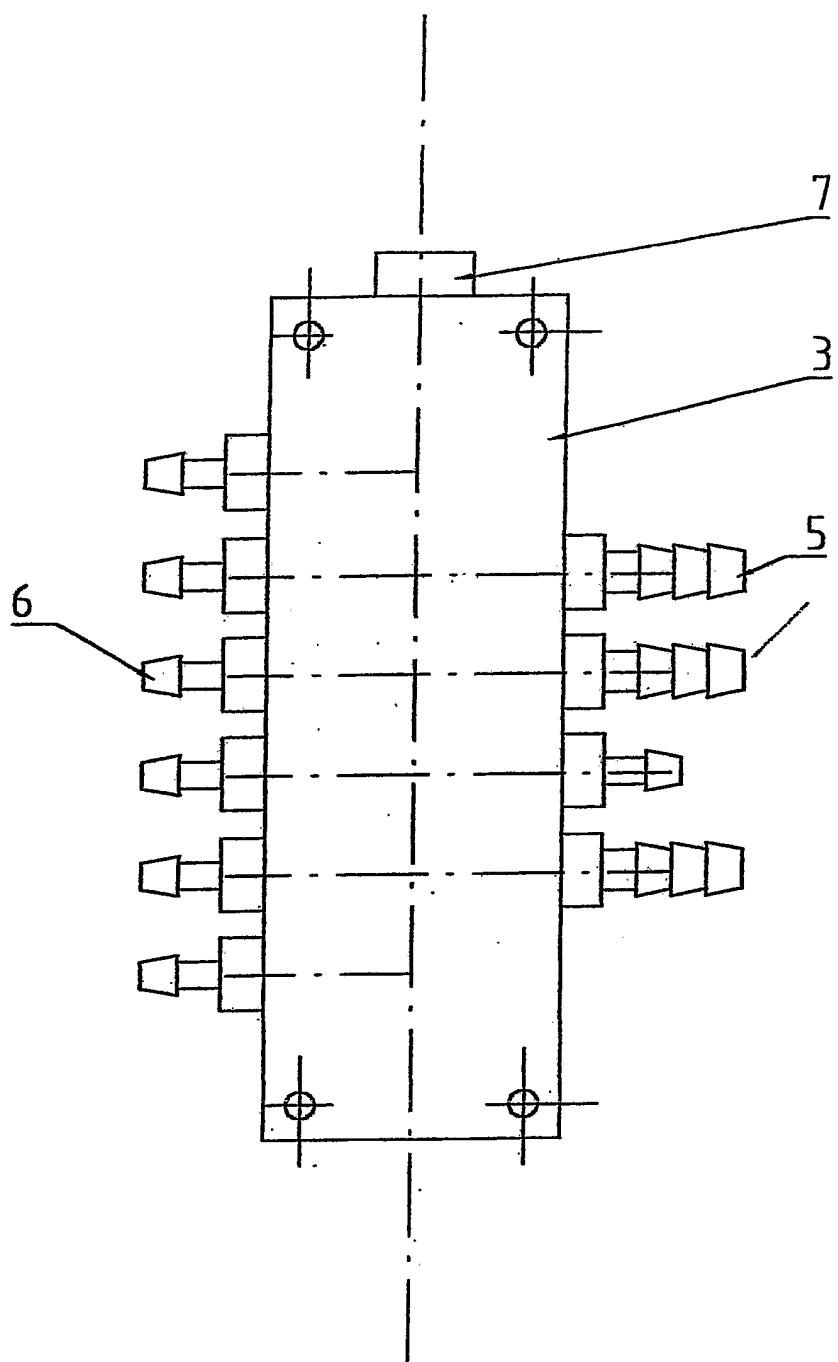


Fig. 2.

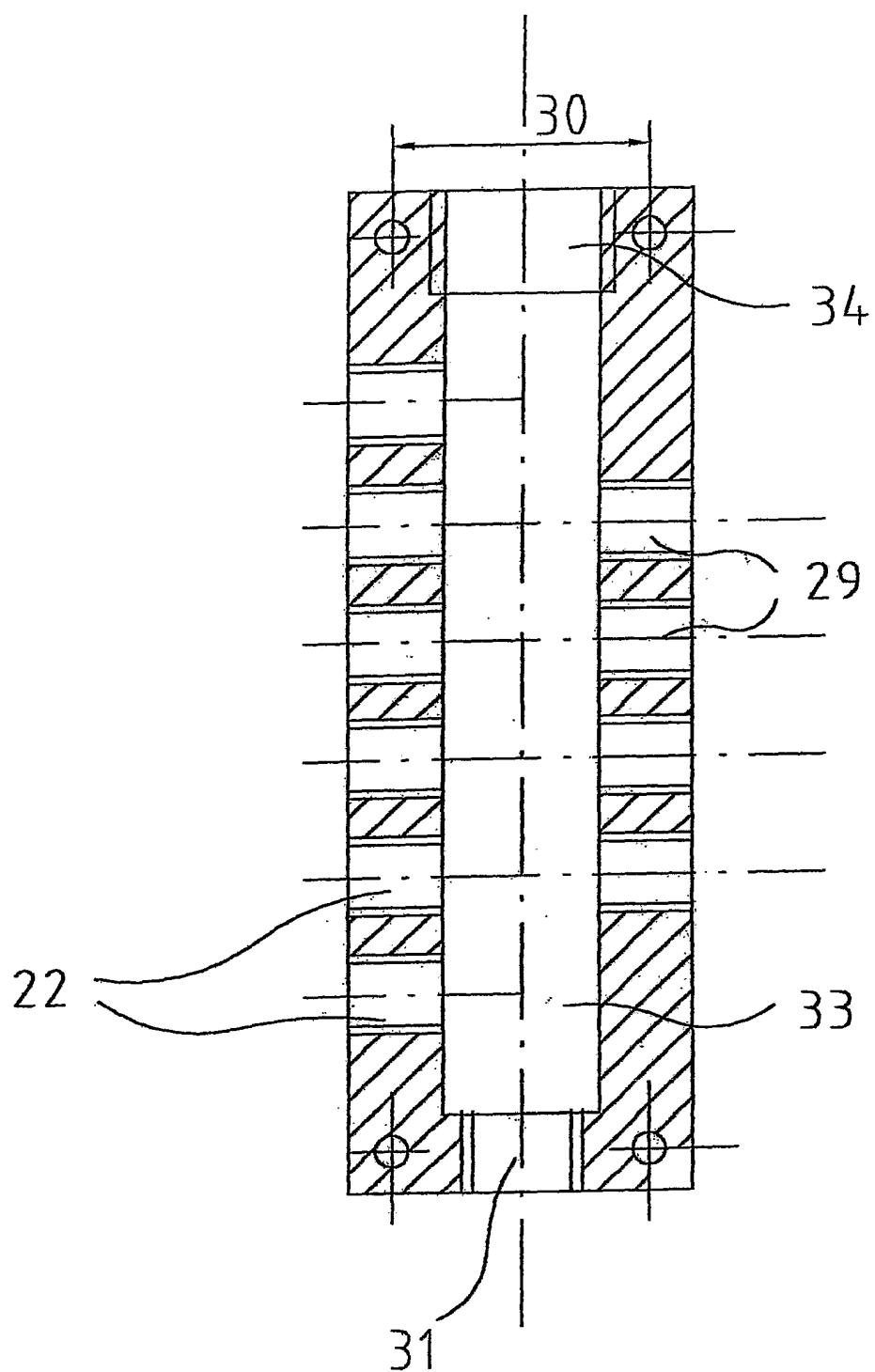


Fig. 3.

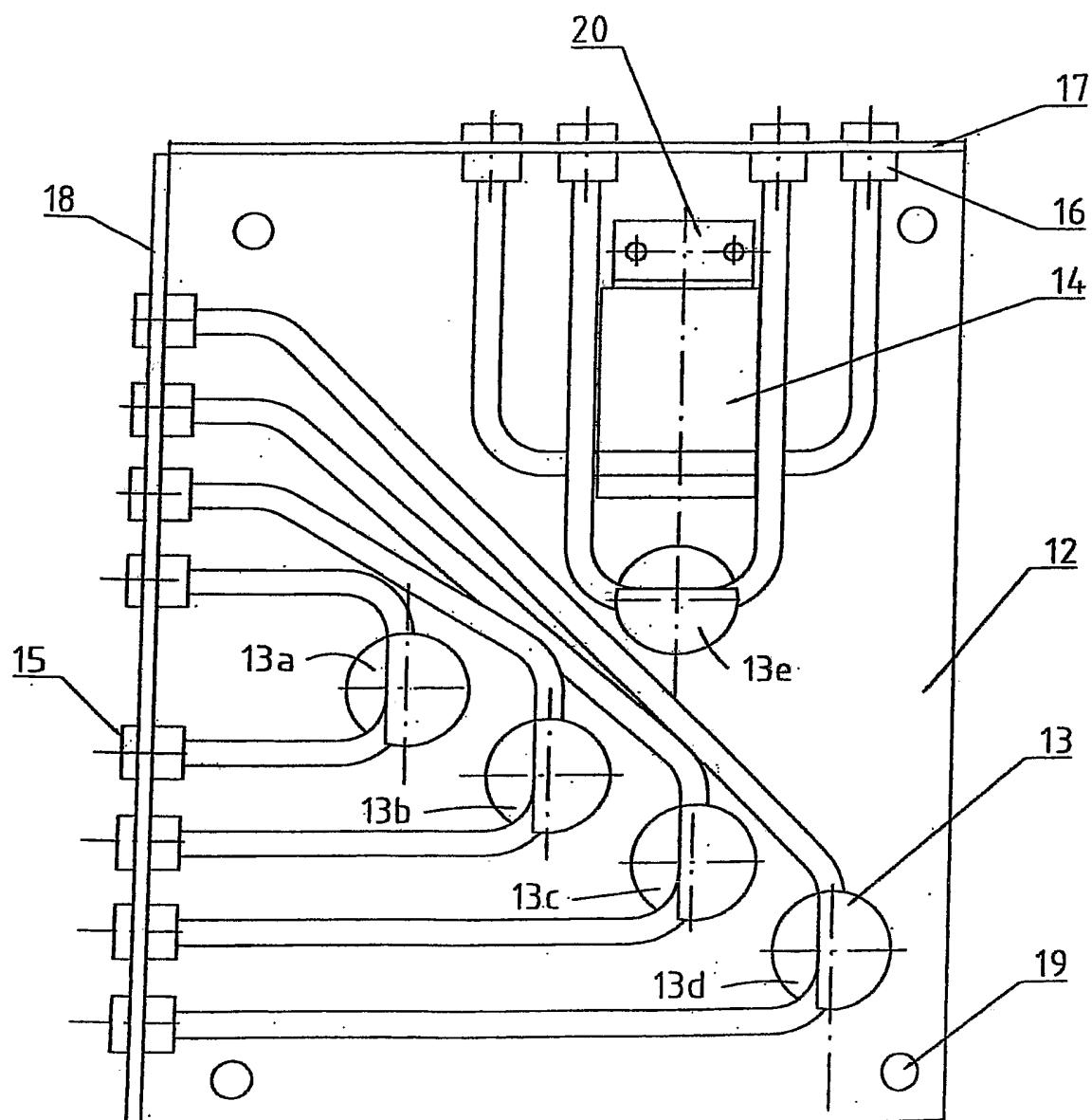


Fig. 4.

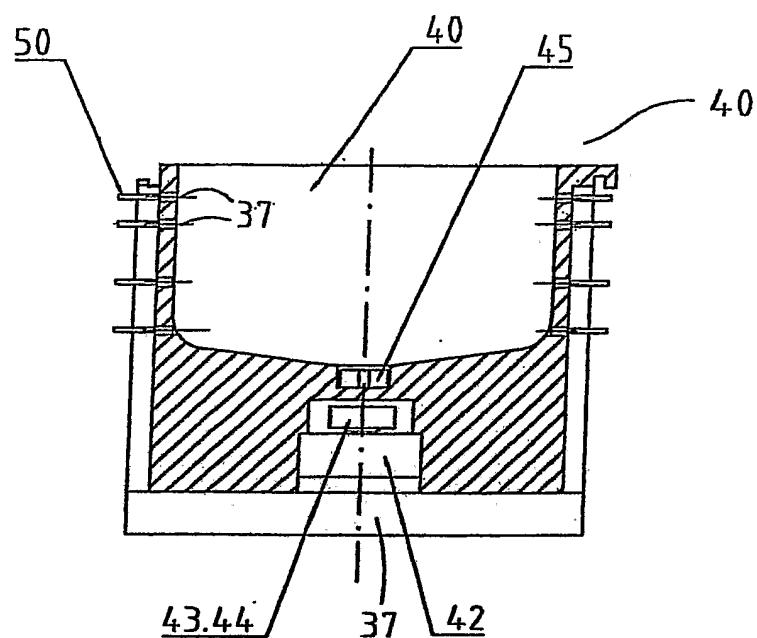
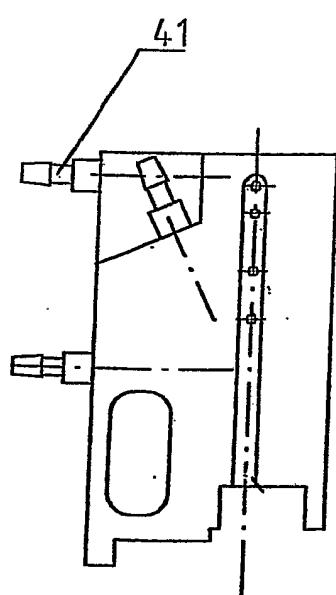


Fig. 6.

Fig. 7.

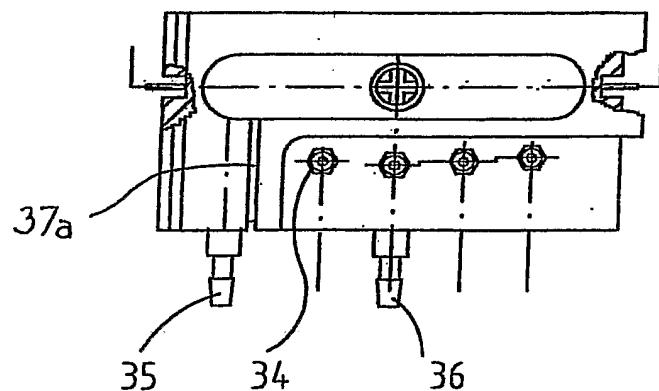


Fig. 5.

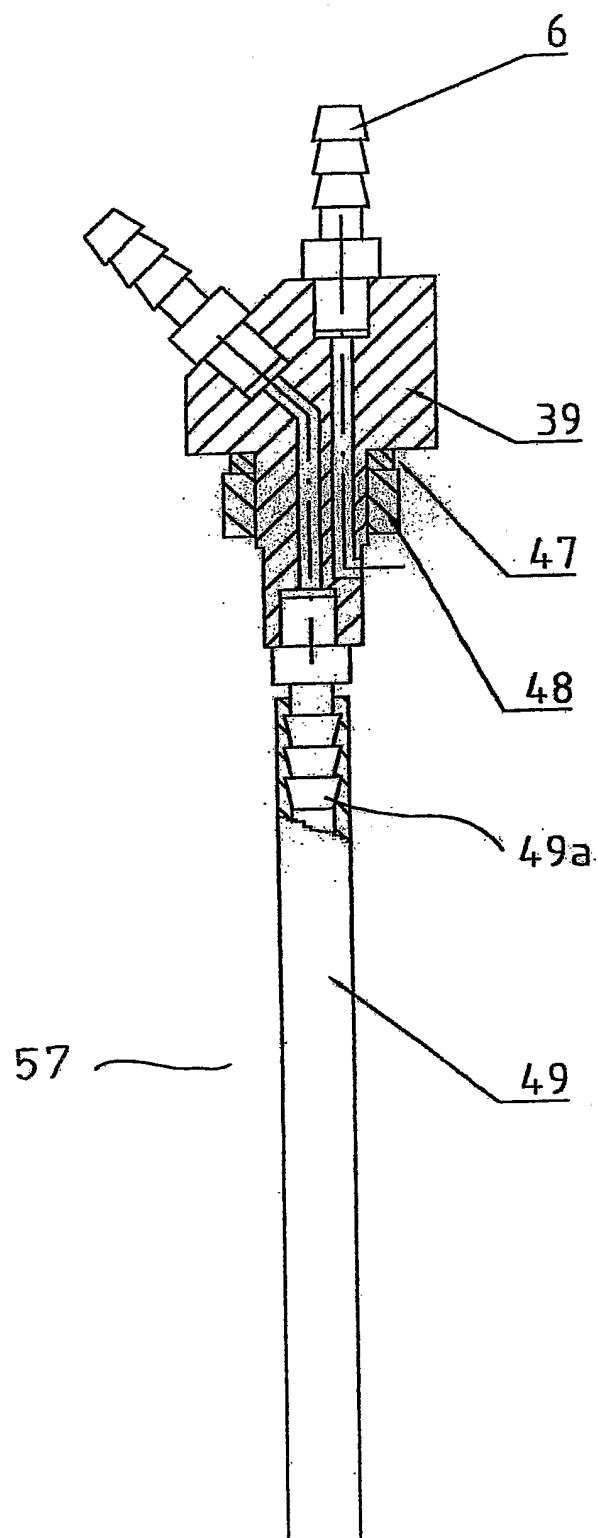


Fig. 8.

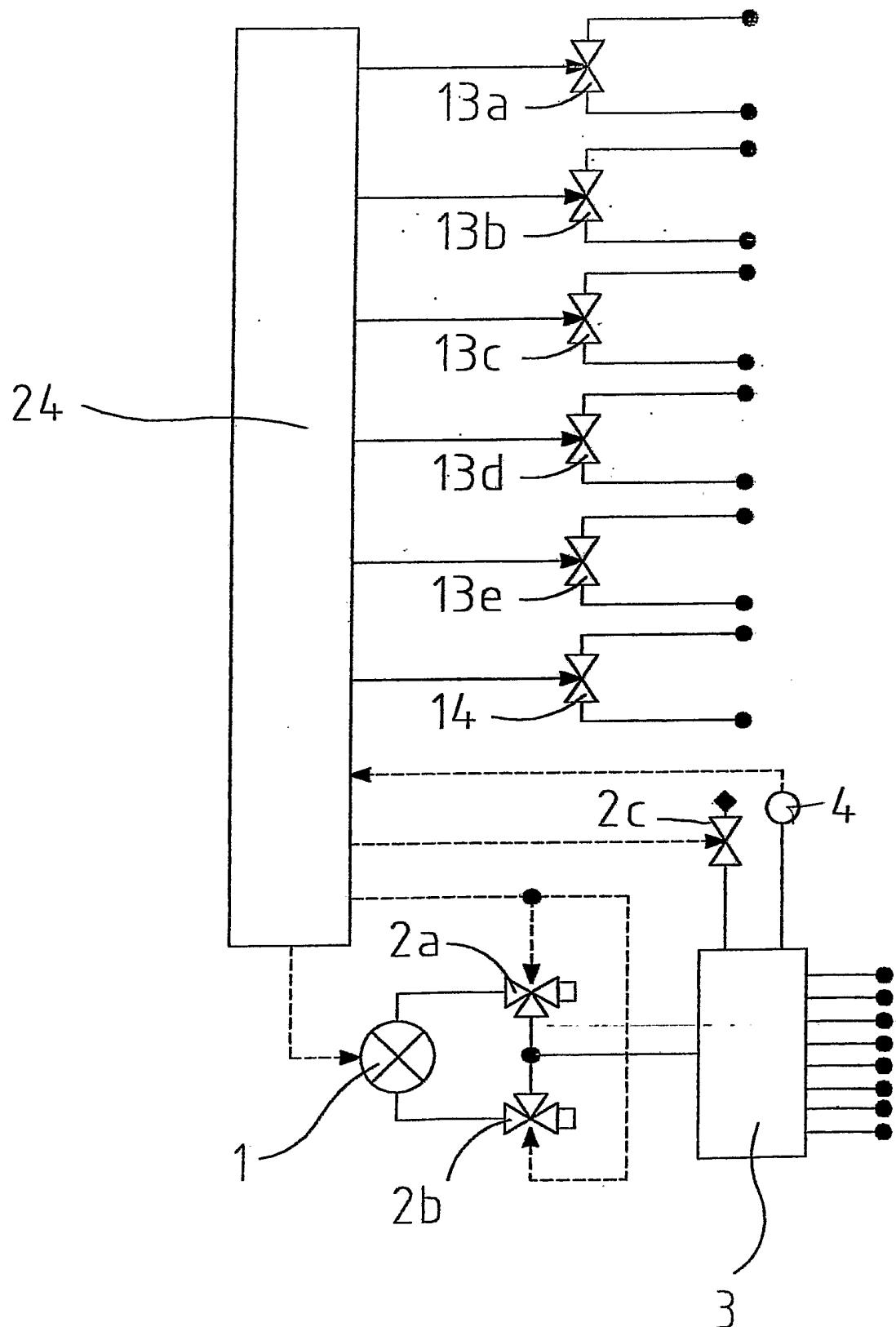


Fig. 9.

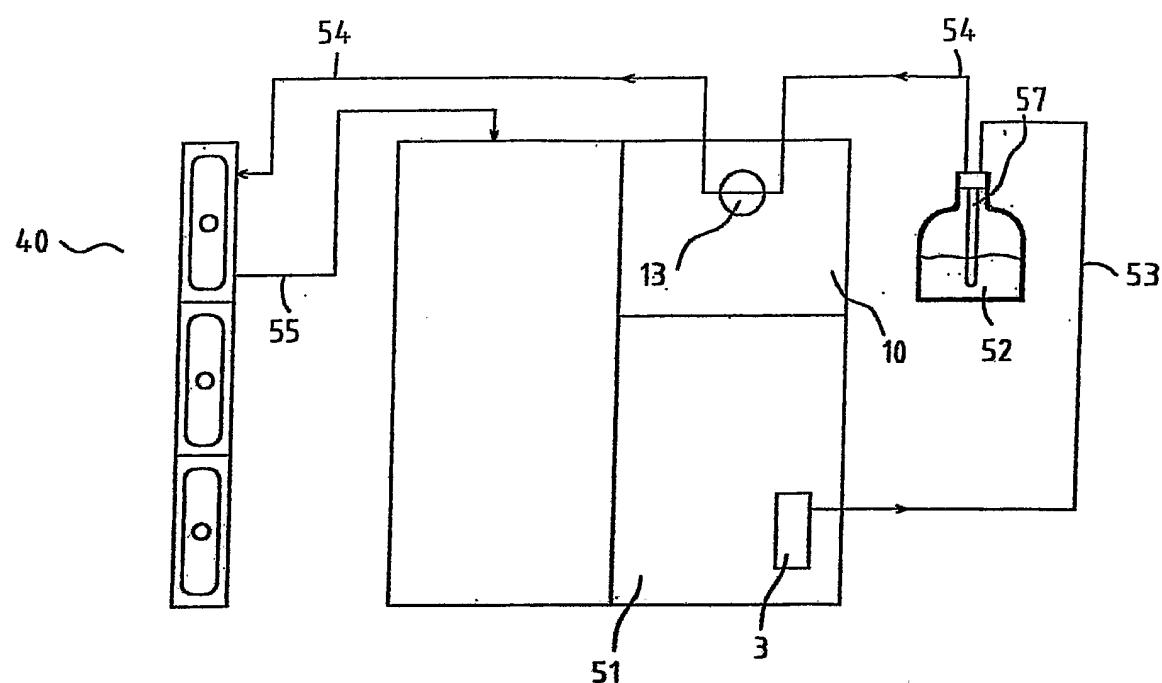


Fig. 10.

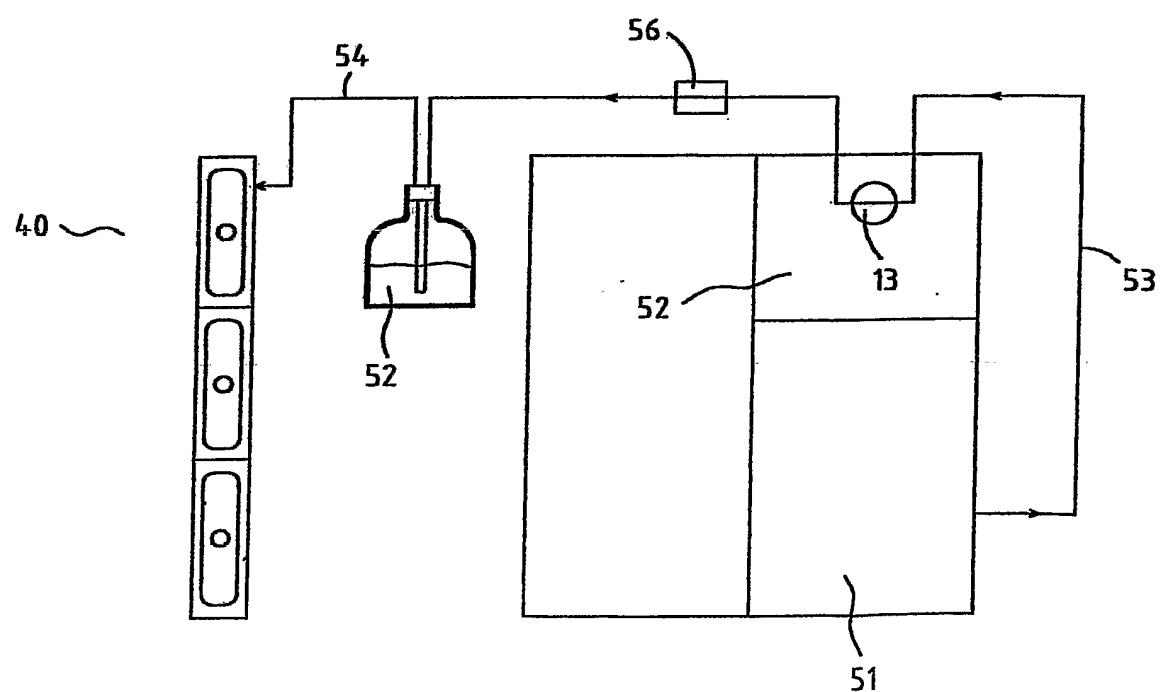


Fig. 11.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 03/00035A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N35/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ^o	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 920 056 A (DASGUPTA PURNENDU K) 24 April 1990 (1990-04-24) the whole document ---	1-13
X	US 4 865 992 A (HACH CLIFFORD C ET AL) 12 September 1989 (1989-09-12) abstract; figure 1 column 2, line 22 - line 60 column 3, line 7 -column 4, line 44 ---	1-13
X	US 4 106 671 A (SHARPLES THOMAS DAVY) 15 August 1978 (1978-08-15) abstract; figures 1,3 column 2, line 65 -column 3, line 50 ---	1-13

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Date of the actual completion of the international search 25 August 2003	Date of mailing of the international search report 04/09/2003
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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 192 984 A (BEECHER GARY R ET AL) 9 March 1993 (1993-03-09) abstract; figure 3 column 6, line 34 -column 8, line 14 -----	1-13
A	EP 0 388 144 A (IRICA INSTR INC ;TAKARA SHUZO CO (JP)) 19 September 1990 (1990-09-19) abstract; figure 1 -----	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/HU 03/00035

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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