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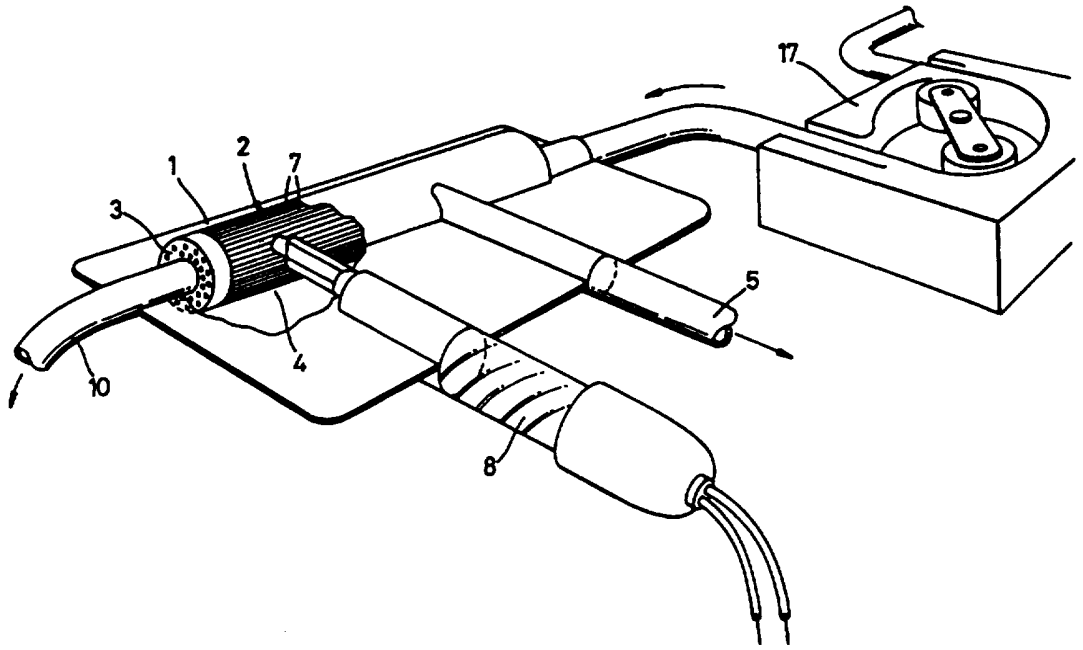

(57) Abstract

The present invention describes a device to process a fluid, the device having a membrane filter, wherein an agent able to detect or cause modification of at least one component of said fluid is localised in said device, preferably on the membrane. The device is arranged to filter the fluid by cross-flow filtration. A preferred form of membrane filter is hollow fibre membrane(s), especially a single hollow fibre membrane. Space between the exterior of the membrane and the inside surface of the outer casing of the device may be completely or partially filled with a solid material, which may contain the agent.

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"Membrane Filter Unit"

This invention relates to the membrane units for filtration or analysis or to support cell culture.

It is known to control chemical and biological processes performed in process vessels by withdrawing samples, filtering the samples to remove undissolved, colloidal or suspended particles or materials of high molecular weight and then subjecting the filtrate to chemical tests. The filtrate may optionally be returned to the mother liquor after analysis. The whole operation may be time consuming and laborious and the quantities of filtrate removed may affect the course of the chemical or biological process. Alternative analytical methods that are available for "real-time" analysis within the process vessel are often highly specific to the particular analyte, provide only very restricted information and may be expensive.

It would be advantageous to have a system that allowed continuous sampling without causing substantial change to the total volume of the process liquor, but which

automatically removed substances over a chosen particle size or over a chosen molecular weight by filtration, and returned the filtrate to the process liquor. It would be especially advantageous if the system involved the temporary removal of only a minimal amount of the process liquor from the process vessel.

Additionally many process liquors contain soluble or dispersed ingredients which require to be separated, combined, monitored, analysed or controlled. These ingredients may be reactants, intermediates or products of the process. However, analysis and/or control are frequently made difficult, or even impossible, by the presence of substances in suspension or of substances of lower or higher concentrations in solution. The problems which arise because of the presence of these substances include obstruction of the membrane pores, discoloration or turbidity of the liquor making colorimetric analysis difficult, and chemical imbalances which make analysis and processing difficult, and contamination, which can lead to the rapid deterioration of, for example, cells and/or sensor elements. Micro- and ultra-filtration membranes exist which allow the separation of particles such as proteins, cells, cell debris and bacteria, from one another, but separation of these materials or substances from one another can be difficult, inconsistent and time consuming. The delay in the response time may be unacceptable.

The above also applies where it is desired to grow cells in culture on a membrane or other support and where the cells or a sample thereof are to be exposed to challenge substances.

The present invention provides a device to process a

fluid, the device having a membrane filter, wherein an agent able to detect or cause modification of at least one component of said fluid is localised in said device, for example is located on or in proximity to said filter.

The device of the invention is arranged so that filtration of the fluid occurs by cross-filtration, ie the fluid to be processed flows along the surface of the membrane and is not directed perpendicularly towards the membrane.

In a preferred embodiment the device of the invention comprises an agent (sensor) able to detect a component in the process liquor, which may be, for example, located in the test fluid.

Optionally, the detected or modified component is released back into the fluid.

The fluid to be processed may comprise a liquid (optionally including dissolved or suspended solid particles). Optionally the fluid to be processed comprises a gas. Alternatively the fluid to be processed is a liquid suspension of cells or parts of cells.

In one embodiment, the device of the invention is for use in a continual processing operation, that is to say a constant supply of the liquid to be processed flows through the device. In this embodiment it is preferred that the agent is self-regenerating, although it may also be possible in certain circumstances for the agent to be artificially regenerated at intervals during the processing operation or even for the agent, optionally together with the filter on which the agent is located,

to be replaced periodically as required. It is possible for the device to be adapted to support cell growth on the membrane, the fluid flowing through the membrane comprising all of the nutrients needed to support cell growth. Such an arrangement provides a useful experimental tool as well as a means of culturing and challenging cells to provide an in vitro diagnosis, for example by subsequent exposure of the cells to antibodies or other challenge substances.

In an alternative embodiment, the device of the invention is arranged for single use applications, such as testing body fluids eg blood, plasma, urine, synovial fluid and the like. Generally the device will be wholly disposable or will be partially disposable for such applications.

Optionally, the membrane may be selected to filter out a particular molecular size range so that only molecules below a certain size are present in the filtrate. The agent may be located on the post-filtration side of the filter where the agent to be modified is present in the filtrate. Alternatively the agent may be located on the pre-filtration side of the filter.

The agent may be located on the filter membrane by any convenient means, for example hydrophobic or hydrophilic attraction with the membrane surface or chemical bonding, such as ionic or covalent bonds. Hydrophobic attachment of the agent may be particularly required for certain embodiments, such as devices known as "electronic noses" which detect the presence and/or concentration of a gas. Preferably, the agent is physically attached to the membrane, advantageously by means of a covalent bond. It may be desirable for

certain agents to be attached to the membrane surface via a spacer molecule so that presentation of the agent is enhanced and/or that steric interference is reduced or avoided.

Optionally more than one agent may be located on the same filter and these agents may act independently of each other on different substrates or may compete for the same substrate. Optionally two or more agents may sequentially modify the same original substrate. Thus the first agent acts on the unmodified substrate, producing an intermediate product. This intermediate product is then modified or detected by a second agent. A similar chain of reactions may be produced with any number of different agents.

For certain applications the agent may be located on the walls of the chamber which collects the filtrate, or may be presented on beads, rods or the like located within the chamber collecting the filtrate. Likewise it is also possible for the agent to be similarly located on the filtrant (unfiltered) side of the membrane.

It is possible for different fluids to be present on either side of the membrane, at least one of the fluids being subject to (positive or negative) pressure so that cross-filtration occurs. At least one component of one fluid is thus caused to move across the membrane and undergoes a chemical reaction with a component of the other fluid. The presence and/or amount of product may optionally be detected by a sensor.

An example of this embodiment is the treatment of effluent containing at least one environmentally unacceptable component, which may be rendered harmless

via chemical reaction or which is to be measured. The required reactant is included in the fluid on the opposite membrane side. Either the reactant moves across the filter or, more preferably, the environmentally unacceptable component moves across the filter. The component may then either be subjected to a chemical reaction following which the end product thereof may either be discharged or collected separately or, if desired, recycled. Alternatively the component may be detected.

The filtration device may use positive or negative pressure to control the ingress or egress of filtration fluid and/or the rate of filtration. The pressure may be reversible to allow "cleaning" of the membrane, extending their working life.

Optionally the material to be sampled contains particulate matter such as cell debris or cells. In this situation the use of controlling pressure may be particularly useful. Where cells are present it may be desirable for the device to be a sealed unit so that the filtration process is totally contained within the filter cell.

In one preferred embodiment the volume between one surface of a membrane and its boundary is at least partially filled with a material. The material may be either porous or non-porous depending on the intended use of the device and the membrane selected for use. Optionally, the volume defined between the membrane and the outer casing may be substantially filled with the material. Alternatively the material may fill separate portions of that volume, thus sub-dividing it into smaller discrete volumes. Suitable materials include polymers (for example polymeric adhesives), especially

light curable or UV curable polymers. Specific mention may be made of light or UV curable polymers available from Ablestick Ltd (for example LCM 32, LCM 34 and LCM 35), Bostick Ltd or Dynax Inc (especially 191M) as being useful in this regard. Non-porous materials include solids through which parts of the filtrate can diffuse, for example gels (such as agar gels) or the like. The material may be introduced in liquid or semi-liquid form and solidified in situ. The presence of the porous material may enhance the speed of the response times in testing for the presence and/or amount of a test substance. The material may be chosen having regard to fluid in the filter cell and any test required.

As an example of this embodiment, a single hollow membrane fibre, or a bundle of such fibres, may be placed into an outer casing. The volume between the inner surface of the casing and the outer surface of the membrane fibre(s) may be filled with the material. The material may be inserted into that volume by injection and/or by capillary action. If required, the material may be cured, for example by exposure to blue light or to UV light. The mother liquor may then be fed down the material-filled volume, with the challenge or test substance being provided via the lumen of the membrane, or vice versa.

Alternatively, if a membrane in the form of a sheet is utilised, the material may fill at least part of the volume between a membrane surface and its boundary, normally the inner wall of the casing or a further membrane sheet.

Where a material is present in the manner described above, it is possible for the agent to be attached to,

contained within or encapsulated by the material.

In addition to a component-modifying agent located on the filter, the device of the present invention may optionally further comprise one or more detecting agents or sensors. The sensor(s) may, for example, monitor the level of modified component and optionally also the level of modified component. In a preferred embodiment the sensors are visually apparent or are arranged to give a visual display of their output (for example through a microprocessor or the like). Any commercially available sensor may be used in the apparatus of the present invention. Prefrred examples include light-emitting, photo-reactive or photosensitive sensors.

Where the outer casing (and if present the material) is optically suitable, it will be possible to use colorimetric analysis to determine whether the test substance is present and/or the amount thereof. Desirably the presence of the test substance will be due to a colour change and it may be preferable in certain circumstances for the outer casing and/or material to be optically clear.

A component-modifying agent may be, for example, an enzyme, antibody, abzyme, a microbe (such as a bacteria or virus), genetic material (such as DNA or RNA), lectin, or any chemical reagent or catalyst, or any combination or functional part thereof. Generally where the agent is a biomolecule it will be attached covalently to the filter via a spacer unit, for example a carbon chain, optionally containing reactive groups, eg acrylic acid or acrylamide or the like. In this situation the agent is advantageously provided with any co-factor or co-enzyme necessary for modification of

the component in the liquid to be processed. The co-enzyme and/or co-factor may either be provided on the surface of the filter or may be included in the liquid being processed.

In a preferred embodiment the component of the liquid to be modified is a sugar and the agent is a sugar modifying enzyme, for example a saccharase.

Where the agent is a sugar modifying enzyme, preferably a sugar degrading enzyme (for example a saccharase), the device of the present invention is adapted to process sugar containing liquids, so that the sugar content of the processed liquid is altered, preferably is substantially reduced.

In one particular embodiment the component is a sugar. For example the component may be sucrose and the modifying agent may be sucrase and thus cause degradation of the sucrose into fructose and glucose.

In a further aspect, the present invention provides a process of detecting or modifying a component of a liquid substrate, wherein:

a. said liquid substrate is filtered by cross-flow filtration through a device as described above, the component being present in the filtrate; and

b. the filtered component is detected or modified by an agent located on a filter in said device.

Alternatively the agent may be located on the flitrate side of said filter.

Optionally said modified component is returned to the

filtrant of the liquid.

The membrane for use in the device of the invention may be of any convenient shape and mention may be made of hollow membrane fibres and flat sheet or tubular membranes. Hollow membrane fibres or bundles of such fibres may be preferred in certain situations since this form permits a relatively large surface area through which filtration may occur. For other applications, however, flat membrane sheets (or bundles of such sheets) may be preferable. The membranes may contain pores of sizes from 0.001 to 30 microns in diameter or alternatively may possess Molecular Weight cut-off values from, for example 100 to 1,000,000 (eg 300 to 100,000, 500 to 1,000) Daltons.

The membrane may be made of any convenient material and the present invention is not limited to the membrane to be used. Generally the membrane will be selected for the filtration size. Ceramic filters, for example, may filter particles of diameter 5.0 μm to 0.1 μm and hollow fibre membranes may filter molecules of 1 mDa to 5 kDa in suitable membranes are available commercially and may be made of polysulphone, cellulose, cellulose diacetate, polypropylene, ceramics materials and/or other co-polymers.

The filtrate chamber may incorporate a sensor or plurality of sensors that produce electrical signals in response to changes in the chemical composition of the filtrate or of the fluid surrounding the sensor, and which sensors may be biosensors. Alternatively the device may comprise an agent able to modify one of the components of the fluid as described above.

The device may be adapted (optionally via a connector)

to form a close fit with syringe needles or syringe bodies. This arrangement may be particularly convenient where the sample to be tested is a biological fluid (eg blood, synovial fluid or the like). The syringe needle may itself be inserted into the device, for example where the membrane is a single hollow fibre the syringe needle may be inserted into the lumen of the hollow fibre. Alternatively the needle may be removed from the syringe and the neck of the syringe connected into the device. The syringe plunger may then be depressed, the fluid in the syringe being expelled into the device and undergoing cross-flow filtration followed by modification and/or detection. Thus, an extremely quick and simple test can be performed to give an "on-the-spot" diagnosis.

The device may be connected with pumps and tubing to form an apparatus arranged so that mother liquor may be continuously pumped through the device for separation and sampling; and in which apparatus there may be provision for returning the process liquor and/or filtrate to the mother liquor.

The flow through the membrane may be directionally reversible so that gel polarisation and/or cell attachment may be eliminated or substantially eliminated thus increasing the control and growth of cells and the operational life of the process system. Alternatively the flow rate may be reversed to increase the rate of reaction occurring at the membrane.

The device of the invention may have no vents to the atmosphere and may provide total containment for the fluids in process. The system may be constructed of materials that permit sterilisation of the system.

The device may in some embodiments have no vents to the atmosphere and provides total containment for the fluids being processed. The device may be constructed of materials that permit sterilisation of the system.

To ensure hydrophilicity of membranes, consisting of hydrophobic materials such as polypropylene, poly carbonate and hydrophobic polysulphone, one should follow the following general guidelines:

1. Use a solvent which wets the membrane and is soluble in water. Usually this is done by using 96% ethanol solution.

2. Fill up the module (ie the interior of the capillaries) with ethanol and keep them filled for at least 10 minutes.

3. Replace the alcohol by water and apply reasonable transmembrane pressure (max. 1.0 Bar) to force the alcohol followed by water across the membrane. Maintain this condition for about 10 minutes. For a module with a membrane surface area of 1.0 m^2 one will require a minimum of 2 litres of water. Measure the flow rate of water.

4. After performing the above steps the membrane should be ready for use.

In order to be able to use the hollow fibre membrane filters over a longer period of time one should follow the general cleaning procedure as outlined below:

1. After each filtration process rinse the hollow fibre membrane filter thoroughly with distilled water followed by an appropriate cleaning

solution: eg Decon-Neutracon Solution (neutral pH) for general cleaning of filters used for proteins and fatty substances. Rinse thoroughly afterwards with distilled water.

2. The procedure should be followed by a rinsing procedure in water.

3. The ceramic filters can be brushed after use to clean the surface of the filter, followed by a rinse procedure with appropriate cleaning solutions and distilled water.

4. The hollow fibre membrane cartridges should be sterilised when applicable with the appropriate technique.

5. The membranes should be kept wetted after use. In order to prevent the fibres from drying out, a 10-20% alcohol solution should be used for this purpose.

One should follow the general guidelines for sterilising filters and other parts of the fluidlines that are in contact with the fluids which are to be processed. Details are to be found in the product guidelines for eg autoclaves and steam sterilisers supplied by various manufacturers. For those filters that will not withstand the higher temperatures as used for heat sterilising various chemical methods are available to sterilise the filters in a safe and efficient way.

1. NaOH solution 4% (60 minutes). Not for use with cellulose or cellulose di-acetate filters.

2. Sterilising fluids for medical dialysing units such as Dialina and Renalin Acetoper.

3. Peractic acid 3%.

4. Formalin 4%.

5. Ethylene Oxide (up to 800mg/l).

In one embodiment of the present invention there is provided a device having a filter cell of low internal volume and provided with an inlet tube carrying the mother liquor (ie. the liquid before processing) from a process vessel. The mother liquor in the inlet tube may, if desired, be raised to a sufficient pressure to cause filtrate to pass through a membrane in the cell into a filtrate chamber of minimal volume and from which chamber an outlet tube may be provided for returning the filtrate to the process vessel. The filtrate in the outlet tube may, if desired, be reduced in pressure by suction to produce the pressure differential required for filtration. The cell should additionally have a second outlet tube on the mother liquor side of the membrane so that the unfiltered residue of the mother liquor may be returned directly to the process vessel. The filtrate chamber may carry in close proximity to the membrane a sensor or an array of several sensors as well as a sampling port for the removal of samples for external analysis. Preferably the sensors may be bio-sensors, optical devices, pH probes, conductivity electrodes or any other devices for analysing the contents of the filtrate. The membranes may be of any of the known ceramic or polymeric micro- or ultra-filtration types in hollow fibre or flat membranes forms.

In one embodiment the device is a processing and handling system for liquids which controls, or removes suspended or dissolved particles and substances in a process liquor by filtration of the liquor through micro- or ultra-filtration membranes and which system may incorporate a direct sensor or plurality of sensors so that specific soluble substances can be analysed without interference with or contamination of the sensors. In the system, control of the process can be made rapidly by microprocessor or computer via a feed-back loop system.

Thus the present invention provides a device for use as a liquid handling system, the device allowing a selective sample from a mother liquor to be taken, which sample is free or substantially free from substances of above or below a chosen particle or molecular size. Desirably the device totally contains all the fluids and materials being processed. The device comprises a flow-through cell containing a micro- or ultra-filtration membrane or a plurality of such membranes arranged for separating ingredients of differing particle or molecular size, and a filtrate chamber in which the filtrate collects.

The flow-through cell may have provision for ingress of unfiltered liquor at higher positive or negative pressure.

In another embodiment, a separating and sampling device for fluids is provided which is capable of taking a selective sample from a mother liquor, which sample is free or substantially free from substances of above a chosen particle or molecular size. The device comprises a flow-through cell containing a micro- or ultra-filtration membrane or a plurality of such

membranes arranged for cross-flow filtration. The device has a filtrate chamber in which the filtrate collects for examination. The cell has provision for ingress of unfiltered liquor at higher pressure and egress of filtered liquor at lower pressure. The membrane or membranes may be in the form of a sheet, of tube or of hollow fibres and may contain pores of sizes from 0.001 to 30 microns in diameter. The membranes may possess Molecular Weight cut-off values from 300 to 1,000,000 Daltons. The filtrate chamber may incorporate a sensor or plurality of sensors that produce electrical signals in response to changes in the chemical composition of the fluid surrounding the sensor. The sensors may be biosensors. Optionally the device may be incorporated along with pumps and tubing into an apparatus arranged so that mother liquor may be continuously pumped through the device for separation and sampling. In such an apparatus there may be provision for returning the filtered liquor and/or filtrate to the mother liquor; and also the flow through the membrane may be reversed in direction so that gel polarisation may be eliminated or substantially eliminated thus increasing the working life of the cell.

By way of example embodiments of the invention and uses therefor are shown in Figures 1-11.

Figures 1 to 5 schematically illustrate various embodiments of the device according to the invention;

Figure 6 is a perspective view of one embodiment of a device according to the invention, with a cut-away section to illustrate the membrane fibres;

Figure 7 is a schematic diagram of a process circuit in

which the device according to the present invention can be used;

Figures 8 and 9 are further schematic diagrams illustrating a device according to the present invention.

Figures 10 and 11 illustrate two embodiments adapted to support cell growth and, optionally cellular challenge.

In more detail, Figure 1 shows the device indicated generally at 1 having a flat sheet membrane filter 2 which separates the flow-through cell 3 from the filtrate chamber 4. Process liquor is pumped at pressure through the cell in the direction shown by the arrow and the filtrate may leave the filtrate chamber 4 by a port 5 which may be fitted with a tap (not shown). Alternatively a further fluid may be input via port 5 and be filtered across membrane 2. An agent may be located on the membrane filter 2, cell 3 and/or in chamber 4.

Figure 2 illustrates a device similar to that shown in Figure 1 and described above. In the device of Figure 2 (shown generally at 1) the filter membrane 2 is in the form of a tube 6. The mother liquor is passed through the lumen of tube 6 (which forms flow-through cell 3), preferably at a controlled pressure, in the direction of the arrow. The filtrate will collect in chamber 4 and may be taken off via port 5 which again may if desired be fitted with a tap. Alternatively port 5 may be used to input a second fluid, either to react with the filtrate of the mother liquor (ie the agent may be present in the second fluid) or to control the pressure within the device.

Figure 3 illustrates a further embodiment, similar to those previously described with respect to Figures 1 and 2. In the embodiment of Figure 3 the membrane filter (shown generally at 2) is in the form of hollow fibre membranes 7 of which two are illustrated for simplicity. The number of hollow fibre membranes may be adjusted from 1 to several hundred depending upon the size of the device. The lumen of the individual fibres are used to transport the mother liquor into the device and thus act as the flow-through cell. The filtrate collects in chamber 4. The ends of the hollow fibres are sealed into the device to prevent the mother liquor entering the filtrate chamber 4 by any means other than by passing across the membrane.

Figure 4 depicts a further embodiment of device 1 with tubular filter membrane 2 as depicted in Figure 2 but with the addition of a direct sensor 8. The sensor 8 may be, for example, a pH sensor, a conductivity sensor or a biosensor. In use the component of interest passes across the membrane filter 2 into the filtrate chamber 4. The pressure differential across the membrane may be controlled via port 5 which may contain a tap or valve. The component of interest may react with or otherwise be detected by sensor 8 which then generates production of an output signal, preferably an electrical, audible or visual output signal.

Figure 5 illustrate three further embodiments of a device according to the present invention. In general the embodiments shown are similar to those described above for Figures 1 to 4, especially Figure 3. In Figure 5A, the membrane 2 consists of a single hollow fibre membrane, having an internal lumen of approximately 1mm. The whole of the volume between the exterior surface of the membrane and the interior

surface of the outer casing 9 is filled with a material 11, such as LCM 32 or LCM 35 from Ablestick, which contains an agent able to react with a component of interest in the mother liquor. In use the mother liquor is passed down the lumen of the hollow fibre membrane 7 and filtrate moves across the membrane surface by cross-flow filtration. The component of interest present in the filtrate then encounters the agent held within the material 11. In the illustrated embodiment the material is solid and the agent is uniformily distributed therein. However a porous material encapsulating the agent could equally be used. The component may either be modified by reacting with the agent or may be simply detected by the agent which may not alter it physically or chemically. For example the agent could be light emitting, photosensitive or photoreactive.

In Figure 5B the material 11 does not entirely fill the volume between the exterior surface of the membrane and the interior surface of the outer casing 9, but leaves a pre-determined volume able to accept filtrate. The agent may be present either in the free volume or else be held within material 11 as described for Figure 5A above. Alternatively two different agents may be present in these separate physical locations.

Although not illustrated, the device of Figure 5B could also be produced having two or more (for example three, four or five) volumes separately filled with material 11 (or with different types of material 11) and separated or abutting each other. Again different agents or different concentrations of agents could be contained in each.

In Figure 5C, the device is as shown in Figure 5B,

except that the device further includes a additional port 5. Port 5 may be used to draw off filtrate, to introduce a second fluid, optionally containing an agent to modify or detect the component of interest or simply to adjust the pressure and thus the flow across the membrane.

In Figure 6, device 1 is fitted with a membrane filter 2 which separates the flow-through cell 3 from the filtrate chamber 4. Process liquor is pumped by pump 17 at positive or negative pressure through the device 1 in the direction shown by the arrow. The filtrate leaves the filtrate chamber 4 by a port 5 and is sensed by a direct sensor 8, for example a pH sensor, a conductivity sensor or a biosensor. Excess unfiltered fluid exits via port 10. In the device illustrated part of the outer casing is absent in order to illustrate the membrane filter 2 used which is shown to consist of multiple hollow fibres 7 as in Figure 3. However other forms of membrane filters 2 can also be used.

Figure 7 shows a process vessel 12 in which cells are being cultured under agitation using stirrer 30 and in which the glucose concentration requires to be continuously monitored. A peristaltic pump 17 pumps the mother liquor from the vessel to an inlet port 13 in a device 1 according to the present invention. The device illustrated is that shown in Figure 6, but any of the other embodiments could likewise be used. Pump 17 maintains sufficient pressure to cause filtration through a hollow fibre membrane filter 2. Within the filter cell is a glucose bio-sensor 8 which measures the quantity of glucose in the filtrate and the filtrate may be returned to the process vessel through outlet tube 14 and the residual unfiltered liquor may

be returned to the process vessel through outlet tube 15.

Figure 8 shows the filter cell incorporated in a working system in which the process liquor is passed by a pump 17 through a pressure sensor 20 to the device according to the invention 1, fitted with a direct sensor 8 which is monitored by a direct sensor assay instrument 16. The process liquor exits from the device 1 through a second pressure sensor 20a and a second pump 17a which is adjusted in pumping rate relative to the pumping speed of the first pump 17 to control the pressure in the device 1. Filtrate accumulates in the filtrate chamber 4 (not shown) and is pumped from it by the third pump 17b by way of a third pressure sensor 20b. The process liquor is returned to the process via connecting tubes (not shown) and the filtrate is directed through a multi-port valve 18 to an external analytical system 19 for further analysis, or to a drain or filtrate store 21, or to a filtrate return line 22 in which it may join the sampled process liquor returning to the process.

Figure 9 shows the device 1 according to the invention incorporated in a working system in which the process liquor is passed by a pump 17 through a pressure sensor 20 to the filter cell 1, fitted with a direct sensor 8 which is monitored by a direct sensor assay instrument 16 which can be microprocessor or computer controlled. The process liquor exits from the device 1 through a second pressure sensor 20a and a second pump 17a which is adjusted in pumping rate relative to the pumping rate of the first pump 17 to control the pressure in the device 1. Filtrate accumulates in the filtrate chamber 4 (not shown) and is pumped from it by the third pump 17b by way of a third pressure sensor 20b.

Within the enclosed circuit of pumps 17, 17a and 17b and pressure sensors 20, 20a and 20b processing of material within the device 1 can be achieved at above and below atmospheric pressure on both sides of the membrane 2 (not shown). The process liquor is returned to the process and the filtrate is directed through a multi-port valve or valves 18 to an external analytical system 19 for further analysis, or to drain or filtrate store 21 or to a filtrate return line 22 in which it may join the sampled process liquor returning to the process. If the process involves cell culture, at the end of the process, mature cells or cells ready for harvest can be flushed out of the circuit and collected via line to container 23. This can be achieved continuously or in discreet batches. The whole system is constructed or materials that can be sterilised.

An additional sampling circuit is illustrated whereby a sample can be withdrawn to testing unit 24 and can either be held in test 25 or returned via pump 17c to the process circuit. Testing unit 24 may be an additional sensor and assay instrument. Alternatively unit 24 may be used to incorporate a substance to the process liquor.

2Figure 10 shows a device according to the invention shown generally at 1, the membrane filter lumen being shown in dotted lines. In the embodiment shown pump 17 pushes cell growth medium around a closed loop made up of line 26 and device 1. Present in line 26 is an outlet means (generally a tap or valve) 27, a sensor 8 and also injection or withdrawal means (here illustrated as syringes, but the invention is not so limited) 28a and 28b. The injection or withdrawal means 28a and 28b may be used either to introduce factors exhausted from the medium due to cell growth or

may take a sample of the medium from the closed loop for analysis. This latter option may be of interest where the cells grown on the medium are producing a factor or substance which is of interest.

Multiple devices 1 according to the invention may be incorporated into a single closed loop arrangement as is shown in Figure 11. The system may be under the control of microprocessor or computer 35. Multiple injection or withdrawal means 28 (illustrated as syringes) are selectively connectible to individual devices 1 by valves 29 in lines 26. The devices can be connected to biosensors 8 and a line 32 including a pressure sensor 33 and a displacement pump 34 can be used to adjust pressure in the circuit. Collection bays 31 can be provided at various locations for collection of filtrate or mother liquor from specific device, as required. The precise layout of any particular system can be different from that illustrated.

CLAIMS

1. A device to process a fluid, the device having a membrane filter, wherein an agent able to detect or cause modification of at least one component of said fluid is localised in said device.

2. A device according to Claim 1 wherein said agent is localised on said membrane filter.

3. A device according to either one of Claims 1 and 2 wherein filtration of the fluid occurs by cross-filtration.

4. A device according to any one of Claims 1 to 3 wherein the device further comprises a sensor.

5. A device according to any one of Claims 1 to 4 wherein the membrane filter is a single hollow fibre or multipe hollow fibres.

6. A device according to Claim 5 wherein the membrane filter is a single hollow fibre.

7. A device according to any one of Claims 1 to 6 wherein the volume between one surface of a membrane and its boundary is at least partially filled with a porous substance.

8. A device according to Claim 7 wherein the porous substance contains said agent.

9. A device according to any one of Claims 1 to 8 wherein the agent is an enzyme, antibody, abzyme, a microbe, genetic material, lectin, a chemical reagent, a catalyst, or a function part or any

combination thereof.

10. A process of detecting or modifying a component of a liquid substrate, wherein:

a. said liquid substrate is filtered by cross-flow filtration through a device as claimed in any one of Claims 1 to 9, the component being present in the filtrate; and

b. the filtered component is detected or modified by an agent located on a filter in said device.

11. A process as claimed in Claim 10 wherein the agent is a cell culture and said component is a nutrient required for cell growth.

12. A process as claimed in Claim 10 wherein the liquid substrate is a waste product and said agent detects or renders harmless an undesirable component of said waste product.

13. A process as claimed in Claim 10 wherein the liquid substrate is or comprises a biological sample and said agent detects a component of said sample.

14. A method of diagnosis, said method comprising subjecting a test liquid comprising a biological sample from a paitent to a process as claimed in Claim 10, wherein said agent is able to selectively detect the presence and/or amount of component within said liquid.

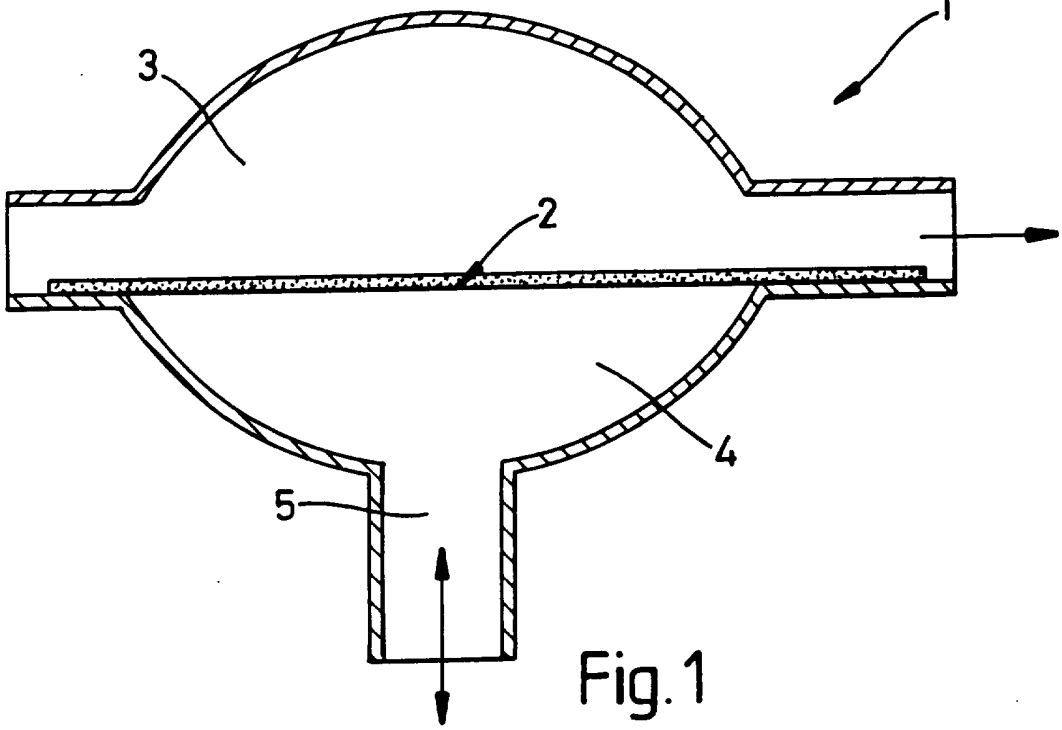

Fig. 1

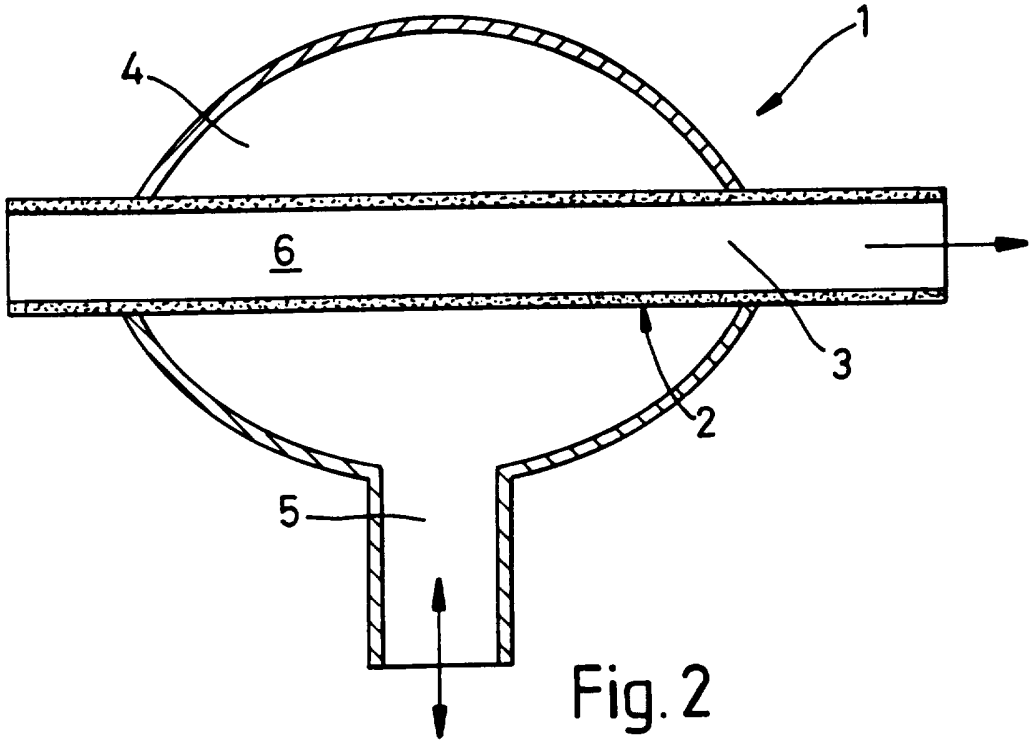

Fig. 2

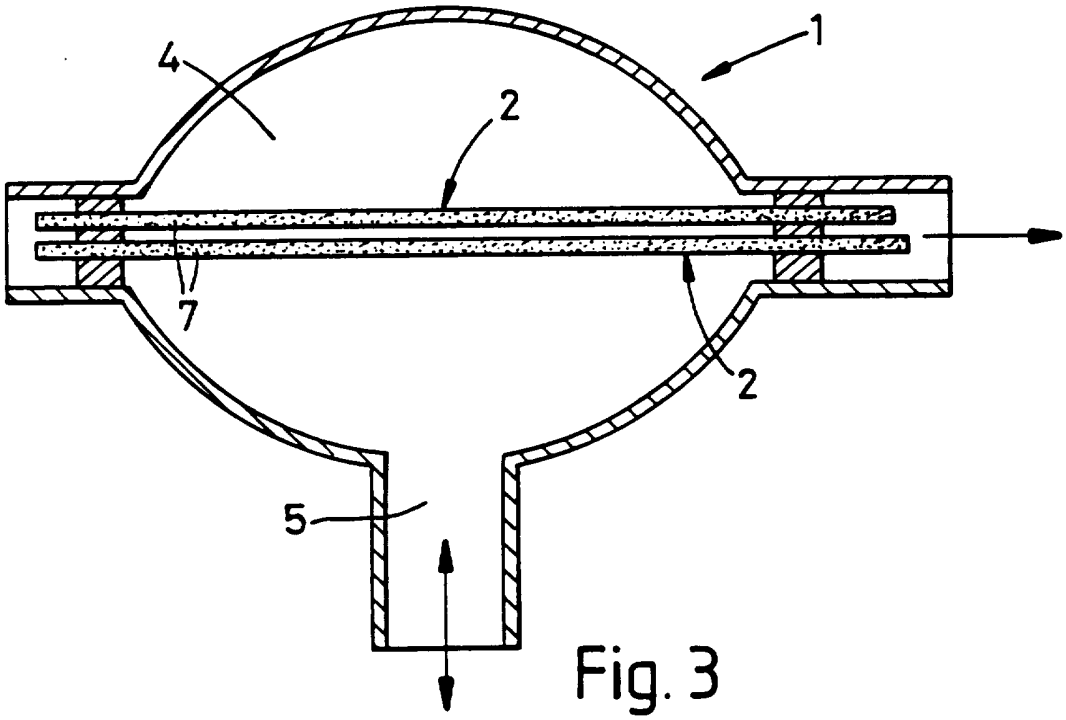

Fig. 3

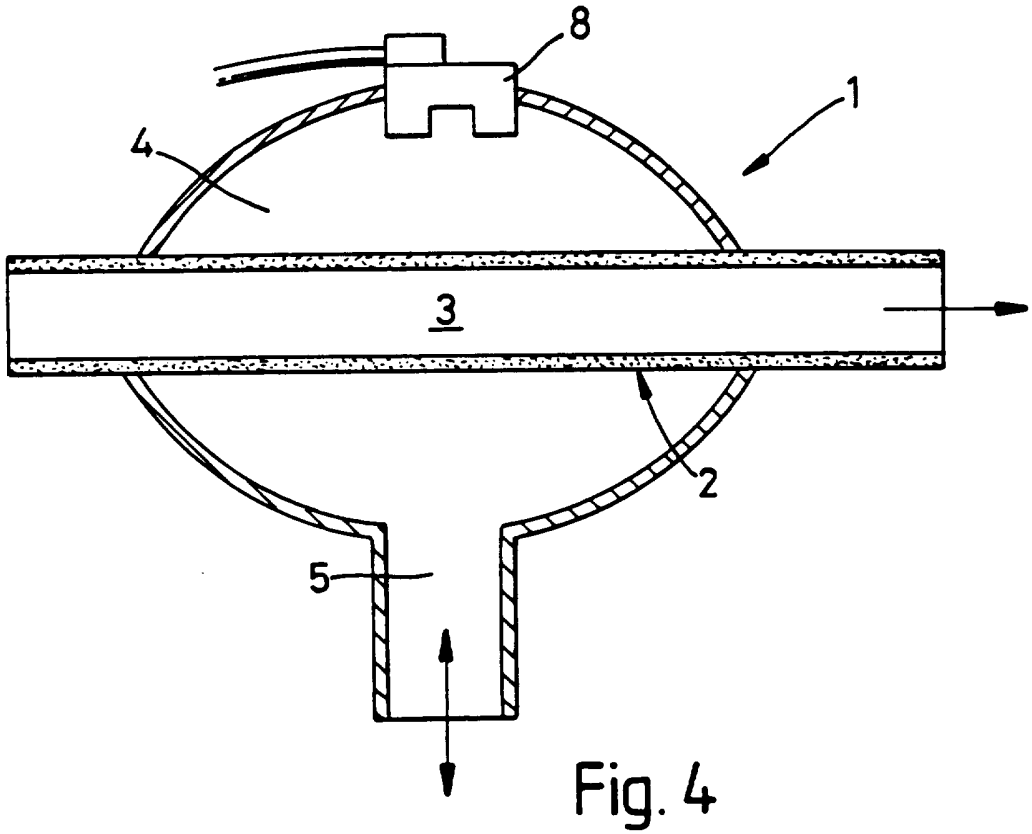

Fig. 4

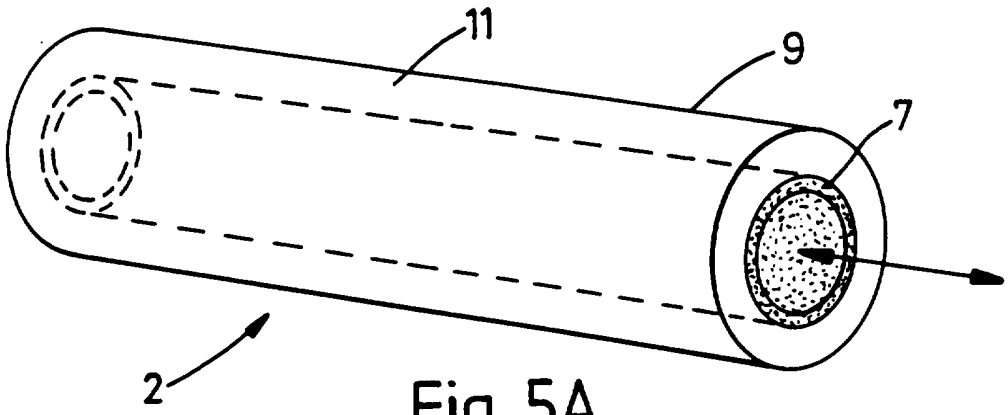

Fig. 5A

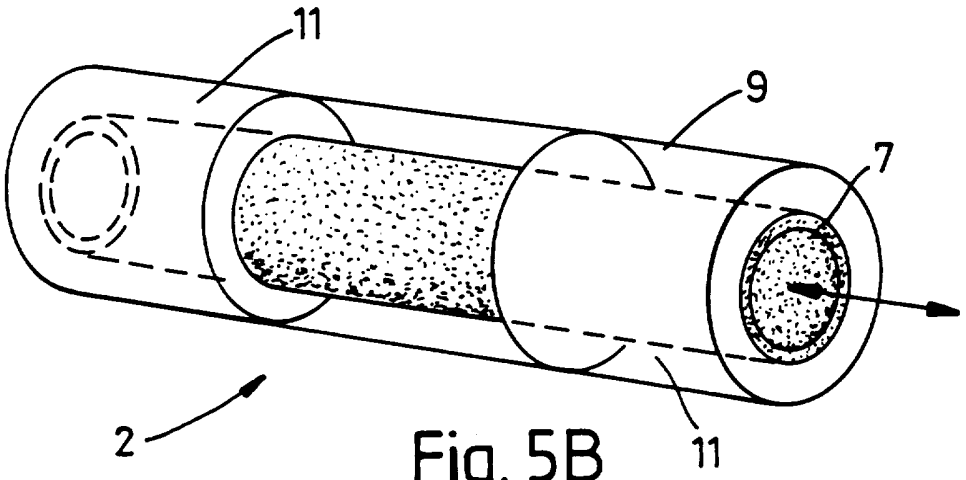

Fig. 5B

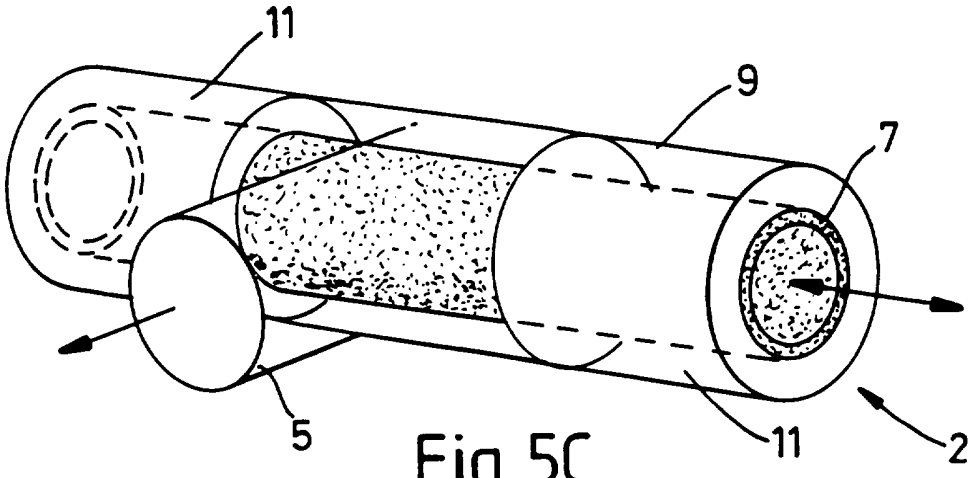

Fig. 5C

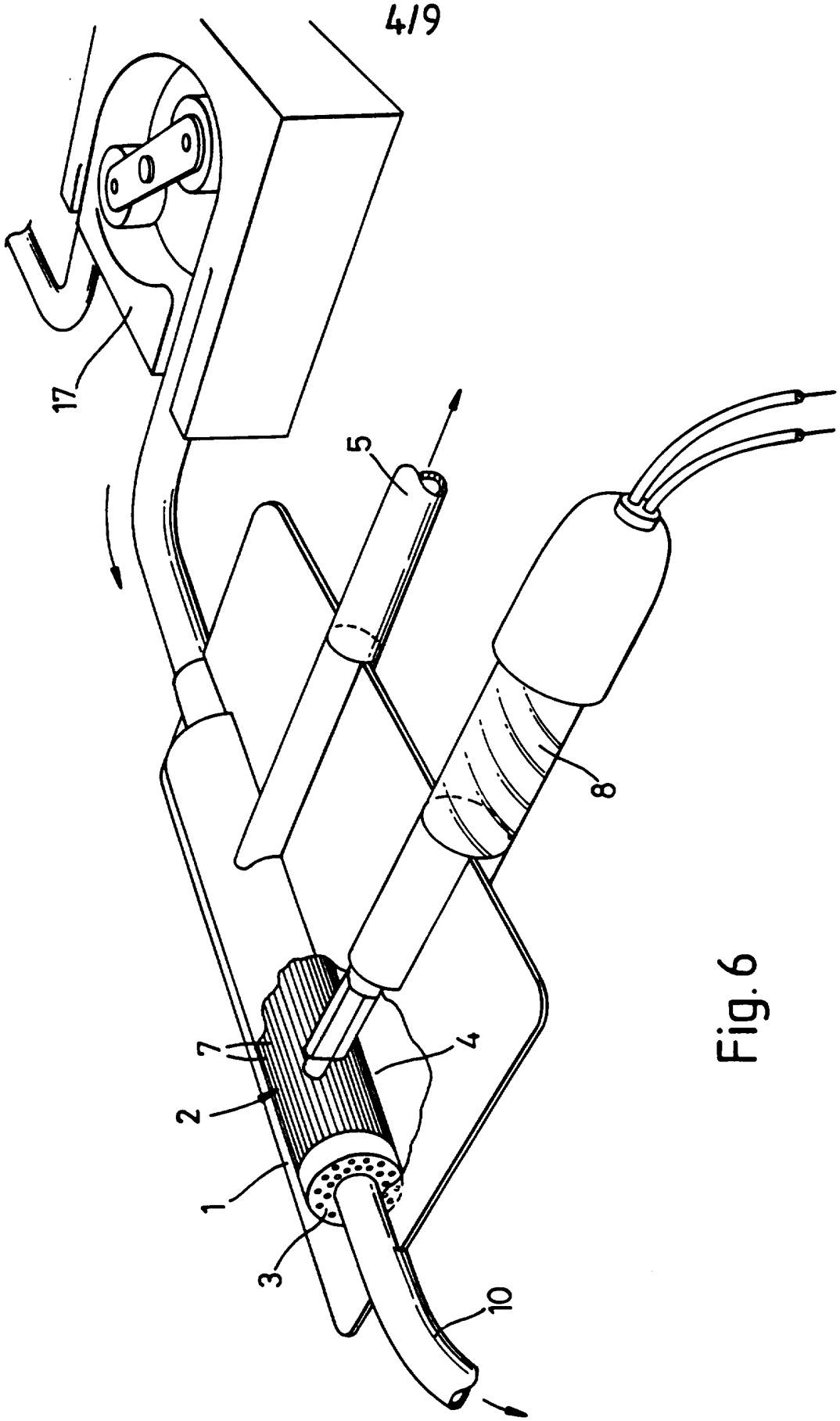

Fig.6

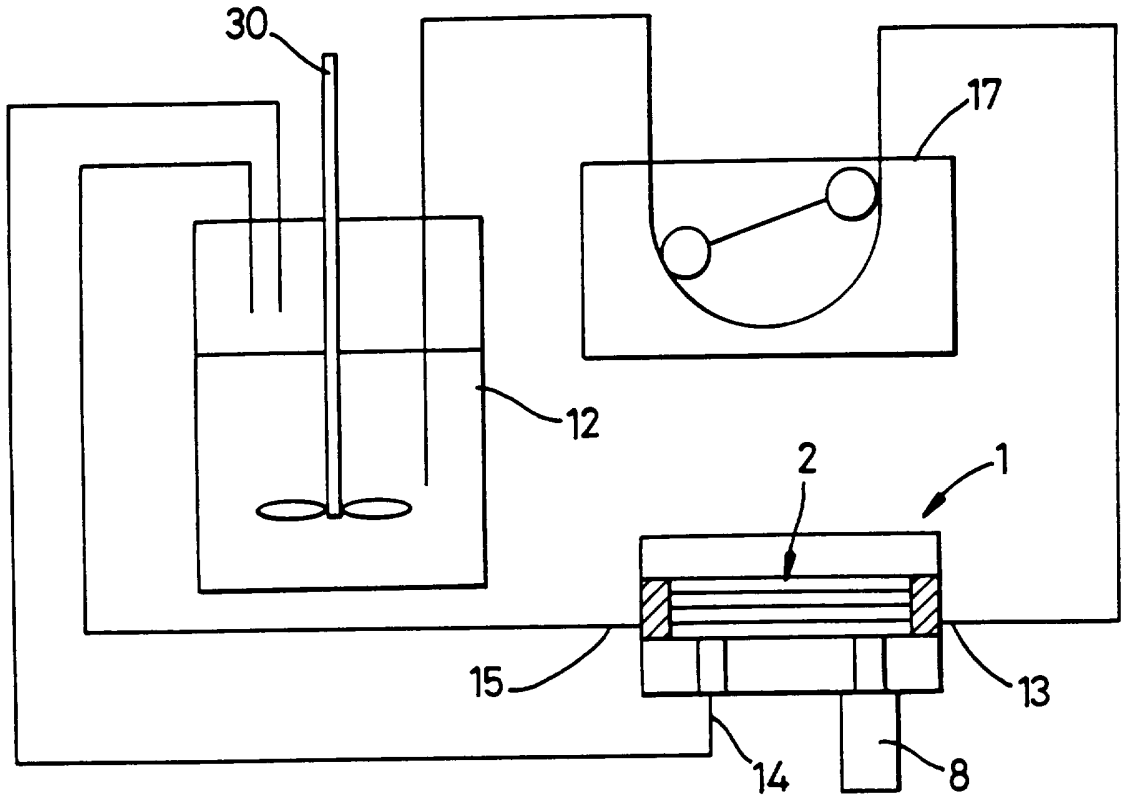

Fig. 7

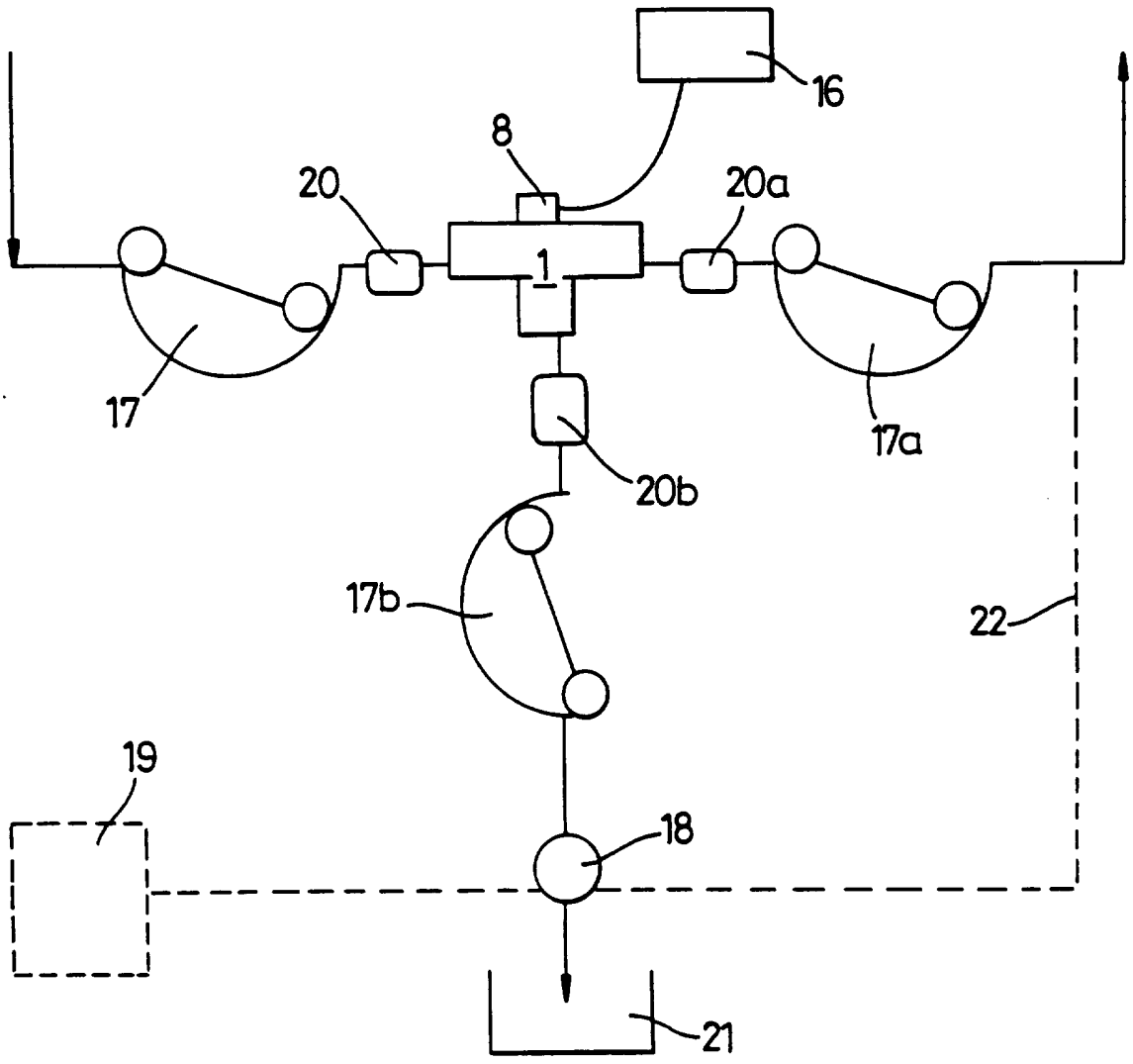

Fig. 8

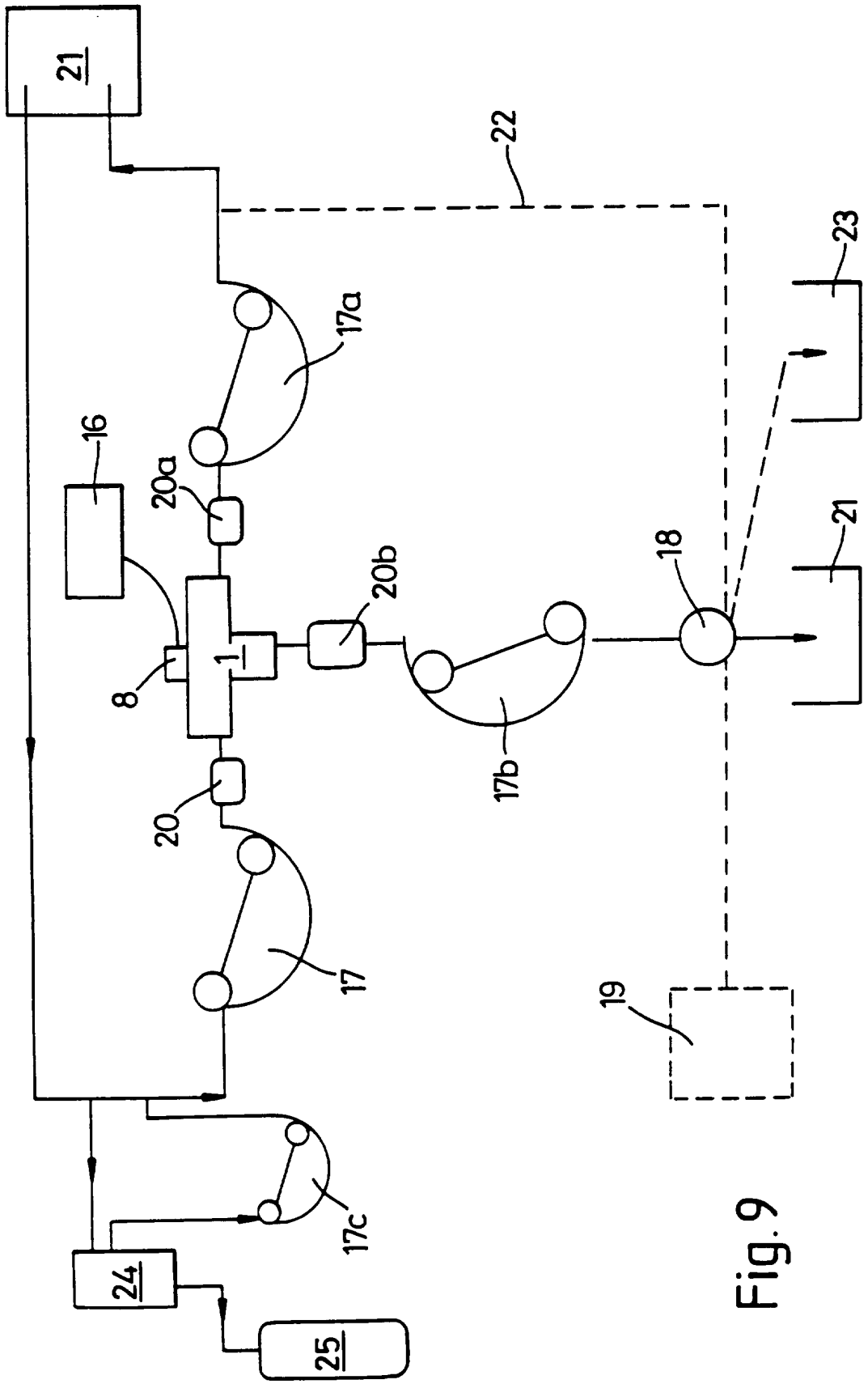

Fig.9

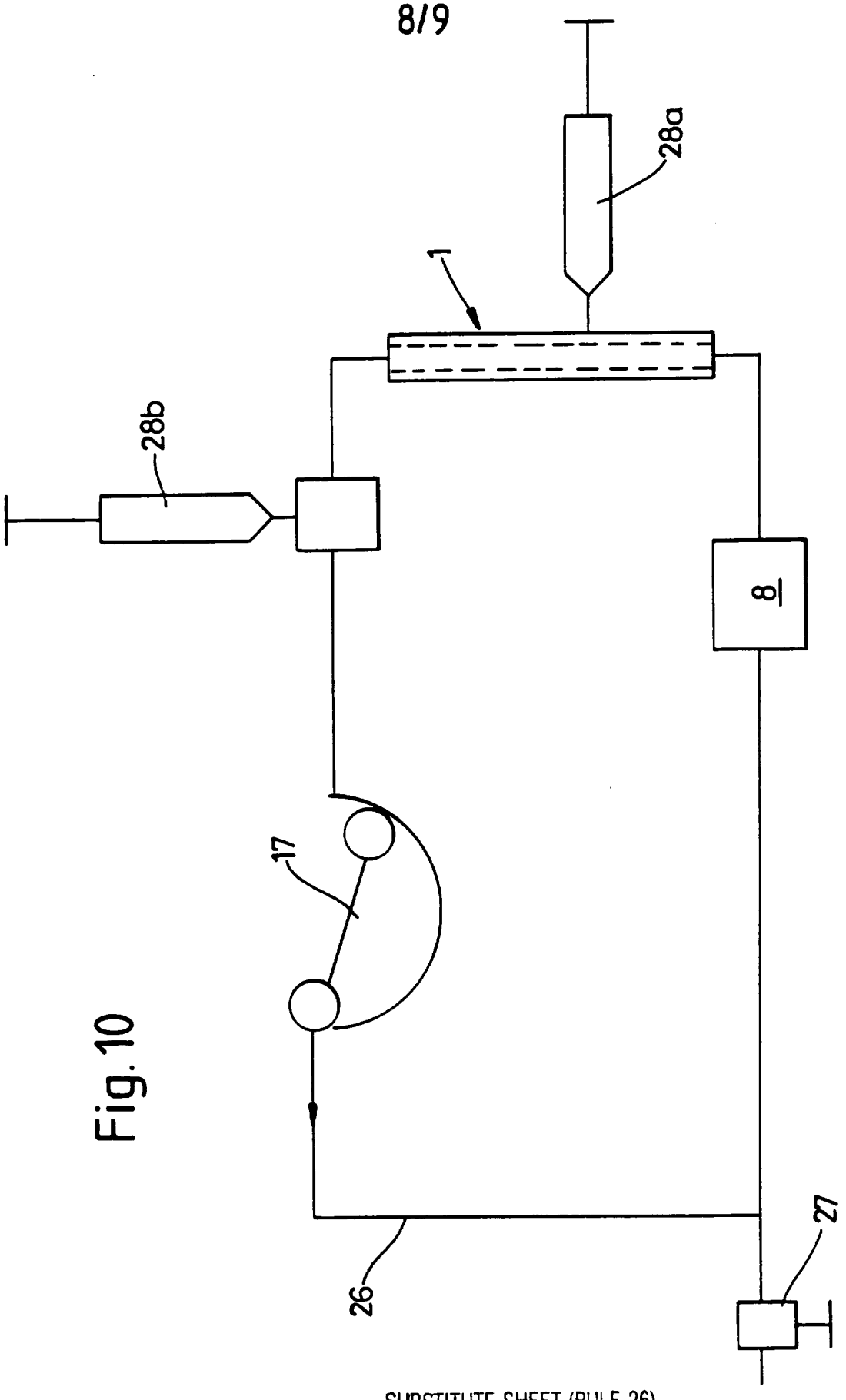

Fig. 10

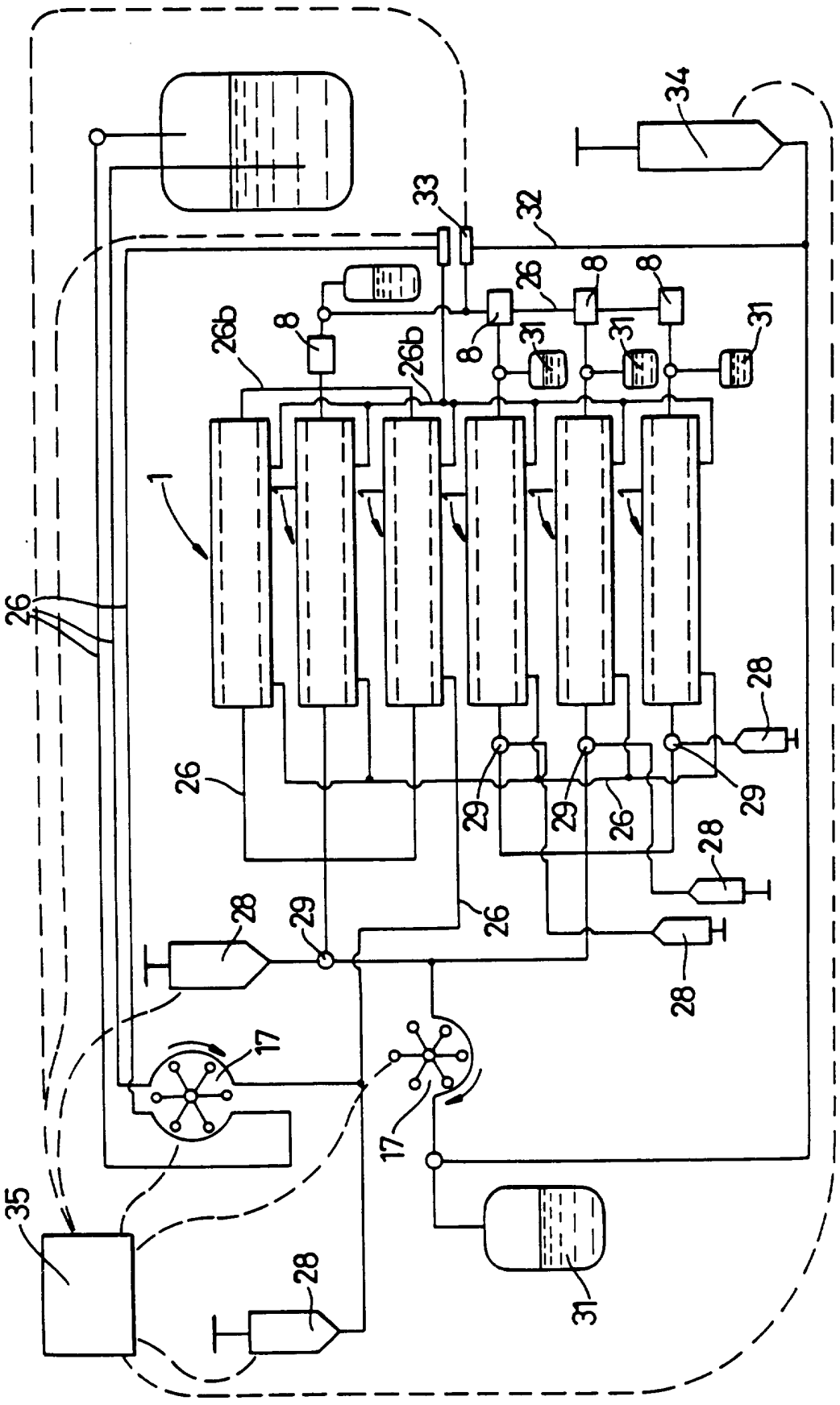
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Fig. 11

INTERNATIONAL SEARCH REPORT

National Application No
PCT/GB 95/01834

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01D61/00 G01N33/48

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 6 B01D

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US,A,4 685 463 (R. B. WILLIAMS) 11 August 1987 see the whole document ---	1,3-6,9, 10,13,14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
28 November 1995	01 -12- 1995

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Devisme, F

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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