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(54) **Fluid handling device for analysis of fluid samples**

(57) A fluid handling method and device for use in analysing a fluid are described. The device has a sample chamber (50, 150) for retaining a predetermined amount of the fluid for analysis in the sample chamber, and a pre-chamber (20, 130). An entry (30) to the pre-chamber requires pressure to inject the fluid into the pre-chamber.

A connecting passage (40, 140) from the pre-chamber to the sample chamber allow flow to the sample chamber by capillary action. This flow can be less sensitive to any variability in the injection. This means the injection pressure or duration, need not be so closely controlled. In turn this can enable simpler or more cost effective apparatus.

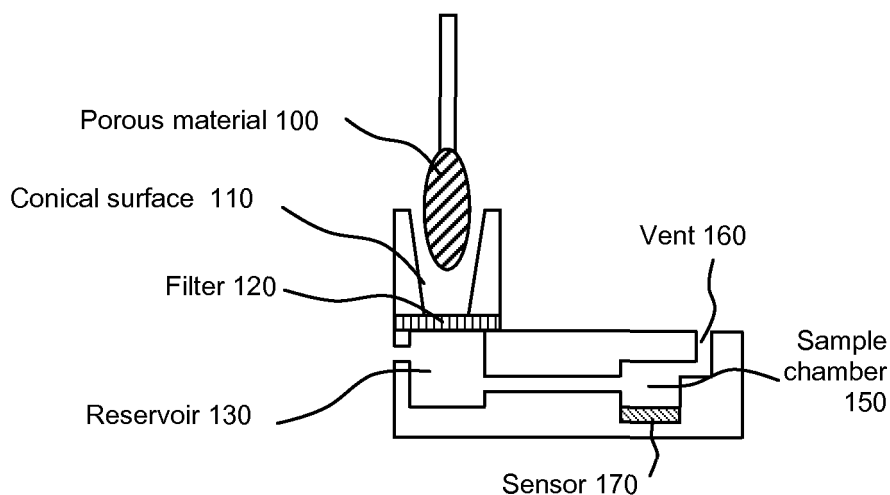


FIG 2

Description

FIELD OF THE INVENTION

[0001] The invention relates to fluid handling devices for analysis of fluid samples, to cartridges having such devices, to systems having such cartridges, and to corresponding methods of manufacturing and using of such devices.

BACKGROUND OF THE INVENTION

[0002] It is known from EP1285628 to provide a device for transferring small blood samples from a patient to a laboratory chip for analysis or to a point of care testing cartridge. A given amount of blood is drawn into a fluid transfer device by capillary action, and the device may be transported manually to a position over an analysis chip. A technician can inwardly press a deformable dimple to provide controlled air pressure upon a channel. This displacement pressure exerts an expelling hydraulic force on the blood retained in the capillary channel. This provides an expelling force to expel a pre-selected known quantity of the blood sample through a tip end on to the analysis chip.

[0003] US patent 6926225 by the present applicant shows a fluid movement system for moving a sample fluid to a sensing element. The sample fluid is first provided into a cartridge, and the cartridge is inserted into a reading device. A pressure variation is provided in the cartridge, and the sample fluid will be moved to a sensing element by using the provided pressure variation. A timing means controls the timing of releasing a pressure in the pressure variation means. The pressure variation means further comprises a resilient member for counteracting against the volumetric variation applied to the volume-variation means.

[0004] US patent 5,096,669 discloses a system with a disposable device and a handheld reader, which can perform a variety of electrochemical measurements on blood or other fluids. In operation, a fluid sample is drawn into the disposable device through an orifice by capillary action. The orifice is sealed off and the disposable device is inserted into the reader. The reader which controls the test sequence and flow of fluid causes a calibrant pouch located inside the device to be pierced, releasing the calibrant fluid to flow across the sensor arrays to perform calibration. Next, an air bladder located in the device is depressed, forcing the sample across the sensors where measurements are performed and read by the reader which performs the calibrations. Once the measurements are made, the device can be withdrawn from the reader and discarded. While in the first step the fluid sample has to be manually inserted into the disposable device, the reader further controls displacing the calibrant fluid as well as the fluid sample within the disposable device.

SUMMARY OF THE INVENTION

[0005] An object of the invention is to provide improved devices for analysis of fluid samples, cartridges having such devices, systems having such cartridges, and corresponding methods of manufacturing and use of such devices apparatus or methods. According to a first aspect, the invention provides:

[0006] A fluid handling device for use in analysing a sample fluid, the device having a sample chamber for retaining a predetermined amount of the sample fluid during the analysis, a pre-chamber for retaining the sample fluid before an analysis, an entry to the pre-chamber being arranged to require pressure for injection of the sample fluid into the pre-chamber, a vent in the pre-chamber, and a connecting passage from the pre-chamber to the sample chamber and arranged to allow the predetermined amount of the fluid to flow to the sample chamber by capillary action. The fluid handling device is preferably a micro fluidic device. The fluid can be a liquid. Compared to known devices allowing injection to the sample chamber, by providing the pre-chamber and the connecting passage to the sample chamber allowing a fluid flow by capillary action, this fluid flow can be better regulated.

[0007] The pre-chamber may be smaller than the amount of the sample and the connecting channel may be arranged to resist fluid flow from the pressure of the injection. Compared to known devices allowing injection to the sample chamber, by providing the pre-chamber and the connecting passage resisting the pressure of the injection, but allowing a fluid flow by capillary action, this fluid flow can be better regulated.

[0008] In either of the cases mentioned above the sample flow can be less sensitive to any variability in the injection. This means the injection pressure or duration of injection or other characteristics of the injection, need not be so closely controlled. In turn this can enable simpler or more cost effective apparatus for injection to be used. This can have the consequences of making the devices more suitable for use by untrained operators, or more suitable for mass production, or for use as disposable devices, or for scaling up to test many samples simultaneously and so on. Compared to known devices having valves and flow rate sensors and controls for metering precisely a flow to a sample chamber, again the features of this aspect of the invention can enable simpler or more cost effective apparatus, with similar consequences.

[0009] The vent may be provided to prevent pressure build-up by injection of the fluid into the pre-chamber when no pressure is required to force the sample fluid from the pre-chamber to the sample chamber. Otherwise the vent may be a further channel that takes any excess sample fluid after the pre-chamber is full.

[0010] Other advantages will be apparent for particular sets of embodiments or any embodiments when compared to different known methods.

[0011] Embodiments of the invention can have any ad-

ditional features without departing from the scope of the claims. Some such additional features are set out in dependent claims and exemplified below. Other aspects of the invention include corresponding methods of manufacturing or using the apparatus.

[0012] Any of the additional features can be combined together and combined with any of the aspects. Other advantages will be apparent to those skilled in the art, especially over other prior art. Numerous variations and modifications can be made without departing from the claims of the present invention. Therefore, it should be clearly understood that the form of the present invention is illustrative only and is not intended to limit the scope of the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] How the present invention may be put into effect will now be described by way of example with reference to the appended drawings, in which:

Fig. 1 shows a first embodiment,
Figs. 2 to 4 show a second embodiment at different stages of operation, and
Fig. 5 shows steps according to another embodiment of the present invention.

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0014] The present invention will be described with respect to particular embodiments and with reference to certain drawings but the invention is not limited thereto but only by the claims. The drawings described are only schematic and are non-limiting. In the drawings, the size of some of the elements may be exaggerated and not drawn on scale for illustrative purposes. Where the term "comprising" is used in the present description and claims, it does not exclude other elements or steps. Where an indefinite or definite article is used when referring to a singular noun e.g. "a" or "an", "the", this includes a plural of that noun unless something else is specifically stated.

[0015] The term "comprising", used in the claims, should not be interpreted as being restricted to the means listed thereafter; it does not exclude other elements or steps. Thus, the scope of the expression "a device comprising means A and B" should not be limited to devices consisting only of components A and B. It means that with respect to the present invention, the only relevant components of the device are A and B.

[0016] Furthermore, the terms first, second, third and the like in the description and in the claims, are used for distinguishing between similar elements and not necessarily for describing a sequential or chronological order. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other sequences than described

or illustrated herein.

[0017] Moreover, the terms top, bottom, over, under and the like in the description and the claims are used for descriptive purposes and not necessarily for describing relative positions. It is to be understood that the terms so used are interchangeable under appropriate circumstances and that the embodiments of the invention described herein are capable of operation in other orientations than described or illustrated herein.

[0018] References to a "chamber" are intended to encompass any size or shape of chamber suitable for retaining the fluid, of any material, rigid or flexible, and can encompass multiple chambers, or a part of a chamber or part of a passageway used as a chamber, or any kind of physical 'room' that can retain fluid or allow, at least temporarily, changing the pressure conditions against its environment. Chamber thus can mean e.g. an entire conduit system but also a more or less separated room only.

[0019] The term 'capillary action' is intended to encompass any kind of capillary forces in order to direct or move fluids in a predetermined way/direction. The connecting passage which allows such action can be in any shape, such as round, elliptical, square, etc. and combinations thereof. The connecting passage may be circumferentially closed like a tube or open like a channel.

Introduction to the embodiments

[0020] The embodiments described relate to types of analysis such as those in which the fluid is injected into a cartridge. In some cases the cartridge can be transported manually to a reader having a sensor. Typically a force is needed to bring the sample into the cartridge, for example to squeeze the sample from a porous medium or to eject a droplet from a bottle or syringe. Additionally, the sample may also need to be forced through a filter, especially when raw sample is used (which is often the case in point of care applications).

[0021] To reduce the complexity of the cartridge it would be favourable if this force could be generated by a simple operator action. But to get an accurate measurement for many types of analysis, the injection of the sample should be very reproducible e.g. with respect to flow rate and total volume. This can be difficult to achieve, particularly with small sample volumes. It could be possible to use expensive precision-engineered parts to assure mechanically that the dosing is reproducible. This would be too expensive for many applications. A way around the precision engineering is to use an autonomous filling mechanism, such as capillary action. However, such mechanisms cannot provide the force required to inject the sample initially or to force the sample through a filter. Hence some of the embodiments show a two-stage sample injection, a pressure driven injection, followed by a separate second stage using capillary action.

Additional features:

[0022] Despite being a fluid handling device, the device can be for use with or may have a sensor for analysing the fluid sample in the chamber. In principle part or all of the sensor could also be on a separate reader device to which the fluid handling device is attached or to which it can be attached or brought into juxtaposition.

[0023] The device can be part of a cartridge for inserting into a reader. This is an arrangement, for which the advantages of simplicity and low cost are well suited. The entry to the pre-chamber can have a filter. This can help avoid contamination of the fluid. The entry can have a receiving surface for a user to press an absorbent material against, to cause the pressure for the injection and to cause release of the sample from a porous sample taking medium (e.g. a cotton swab). This can be convenient for the user. The receiving surface can be conical to drain into the entry. This can also assist in creating more pressure for the injection.

[0024] The entry can have a mechanical injector. The entry can have a one way valve. The entry can be above the pre-chamber. The sample chamber can have a valve to restrict the flow when it reaches the vent. The vent may be located so as to enable the predetermined amount of the fluid into the sample chamber.

[0025] The device may be a microfluidic device.

Embodiments:

[0026] The present invention provides at least two different ways to decouple the pressure (required for entry of fluid into the pre-chamber) from the sample transfer to the sample chamber.

1. In the first apparatus and method a pre-chamber is at atmospheric pressure. In this situation the liquid is squeezed from porous material and ends up in the pre-chamber, which can be substantially larger than the amount of sample. Air can leave the pre-chamber through an air vent channel in the pre-chamber and there is no pressure build-up at all or only minimally. Optionally or alternatively, excess fluid can also leave the pre-chamber through an optional liquid venting channel to avoid pressure build-up. By capillary forces the liquid is sucked from the pre-chamber into a connecting passage and ends up in a sample chamber. So the connecting passage between the pre-chamber and a sample chamber does not need to resist any (significant) pressure.

2. In a second apparatus and method the pre-chamber is much smaller than the amount of sample. The pre-chamber is connected to two channels, one is the connecting passage to the sample chamber and the pre-chamber is vented by the second channel serving as a waste channel that serves to take up or absorb or remove excess liquid. The connecting passage is significantly smaller (typically at least 3 times)

in diameter than the waste channel. During the squeezing action there is now pressure build-up in the pre-chamber and the liquid is split between the connecting passage and the waste channel. In this case the connecting passage may have to be dimensioned such as to resist some of the pressure during the squeezing. However, when the channels are dimensioned appropriately only a small fraction of the connecting passage fills during the squeezing action. After the squeezing has stopped, the connecting passage and the sample chamber will fill by capillary action.

[0027] These different methods and devices will be described in more detail below.

Embodiment of figure 1

[0028] As shown in the example of figure 1, there is an injector 10 of any suitable type, including manual, pneumatic, hydraulic, electrical or mechanical, separate or incorporated into the fluid handling device in the form of a cartridge 80. The device has a pre-chamber 20, an entry 30 to the pre-chamber, a connecting passage 40 for capillary flow to a sample chamber 50, a first vent 25 to release pressure from the pre-chamber. A reader 60 has a sensor 70 provided close enough to analyse the fluid sample in the sample chamber, when the device is located adjacent to or attached to the reader, such as by insertion into a slot for example. Optionally, the sensor can be in the cartridge and the reader used to receive and process readings from the sensor. In operation, the injector injects the fluid into the pre-chamber. Optionally, the entry to the pre-chamber has a filter, so that the injection causes the sample to be forced through the filter. Then the sample ends up in the pre-chamber which functions as a reservoir (and hence to store excess fluid) to which the capillary uptake channel is connected. The pre-chamber is vented by any suitable means, e.g. via a first vent, to release the fluid or air pressure build up by forcing the sample into the pre-chamber. The dosing or metering of the sample flow can be regulated by appropriate dimensioning of the capillary uptake channel, for example in terms of diameter, length, bends and so on, for a given viscosity of the fluid. Such a channel can have a width, for example, between 0.1 and 5 mm, more preferably between 0.5 and 2 mm, and a height of between 10 and 1000 microns, more preferably between 50 and 200 microns. The cross-sectional area of the channel determines the filling of the channel in any orientation, even against gravitational forces. The length of the channel can be between 1 and 100 mm, more preferably between 5 and 15 mm. The volume of the sample chamber is preferably in the order of a few microliters. The cross-sectional area of the capillary uptake channel is preferably 3 times smaller than the cross-sectional area of the pre-chamber that receives fluid during the sample injection. In this way the fluid will fill the pre-chamber through

the capillary uptake channel without building up pressure in the sample chamber during the sample injection time. Optionally the dosing can also be regulated by stopping the liquid flow with a second venting hole, which makes it very reproducible.

[0029] The advantages of this embodiment are many, including:

- the required force for injection can be applied by the operator, which enables the cartridge and reader to be simpler and therefore more cost effective than if precise injection is needed,
- sample injection and filtering is mechanically decoupled from the second part of the cartridge, which makes the characteristics of the injection non-critical to the dosing and
- by using capillary action for the dosing, it can be made reproducible with respect to flow rate and/or total volume.

Embodiments of figures 2, 3, 4 and 5

[0030] In the embodiment of figures 2-5, three cross section views of a cartridge are shown at different stages of operation. In figure 2 the sample is contained in a porous medium (e.g. a cotton swab). In figure 3 the sample is squeezed through a filter into a reservoir by operator action. In figure 4 the sample chamber of the cartridge is filled autonomously by capillary action. Figure 5 shows method steps corresponding to this or other embodiments.

[0031] The sample is contained in a compressible piece 100 of hollow or porous material. By operator action the sample can be squeezed from the hollow or porous medium, in this case by pressing against a shaped receiving surface 110 above a pre-chamber in the form of a vented reservoir 130. The receiving surface 110 may be conically shaped. The receiving surface may be adapted for finger operation, e.g. in size and operative pressure. At the bottom of the conical surface a filter 120 can be placed through which the sample is forced in the same squeezing action by the user pressing downwards. The liquid is then collected in the vented reservoir 130. This is connected to an interconnecting passage 140 in the form of a micro-channel which draws sample fluid from the reservoir by capillary action to fill the sample chamber 150. At the end of the micro-channel and near the top of the sample chamber, a vent 160 may be located, which stops the filling process thus achieving accurate metering. The vent can be implemented via a nozzle to external (i.e. to the environment or the outside world). When fluid enters the nozzle a curved fluid front will form. The curved fluid front now needs to increase its area and reduce its curvature to continue flowing to the outside world (i.e. wetting the cartridge on the outside). This will not happen because a capillary force at the other end of the capillary uptake channel counteracts this further flow. The capillary force balance shifts to the internal end of

the uptake channel. The capability to stop the fluid flow can be improved by making the outside of the cartridge around the venting hole hydrophobic compared to the inner channel walls. A sensor 170 is arranged adjacent to the sample chamber, in this case underneath. The sensor may be separate from the sample chamber, i.e. in another device or integrated with the sample chamber. The entry 30 may optionally have a one way valve (e.g. implemented by rubber flaps or a septum) to avoid spillage and to regulate the pressure needed for injection, to reduce the risk of unwanted contamination.

[0032] Figure 2 shows the fluid in the porous material before the user injects it by pressing downwards. Figure 3 shows the same embodiment with the user pressing the porous material and capillary action starting. Figure 4 shows the same embodiment after the capillary action has filled the sample chamber and the vent has stopped further flow. In Figure 5, step 200 shows injecting fluid into the pre-chamber without pressured flow into the sample chamber. Step 210 shows using capillary action to cause a predetermined amount of fluid to flow into the sample chamber. Step 220 shows analysing the sample in the sample chamber. In principle once the sample has been isolated in the sample chamber, it could be moved if desired to another chamber or other location for the analysis.

[0033] The device as described above may be a microfluidic device. The microchannel dimensions such as diameter, cross section, length and bends, can be set as desired to cause the pre determined flow rate or volume to suit the sensor and according to the viscosity of the fluid. Preferably the dimensions of the microchannel are chosen such that the channel fills in any orientation for the biological fluids that need to be measured.

[0034] The present invention includes an arrangement of multiple sample chambers that can be arranged to be accessible from one pre-chamber to enable many different tests, or many instances of the same type of test to enable averaging. Many pre-chambers can be arranged on one substrate to enable multiple tests. The substrate can have other fluid handling elements such as valves, pumps, mixers and splitters to enable more complex tests to be carried out on the same sample or on other samples. Other types of injectors can be used to provide the pressure. Any type of sensor can be used including optical, mechanical, magnetic or electrical detection types. The sensor can be part of the cartridge or separate. The readings of the sensor can be shown on the cartridge, or transferred to a separate reader or processing system for further processing for example.

Applications and concluding remarks

[0035] Analysing fluids for biological or chemical molecules or constituents can take many forms, such as optical or electrical detection types. Applications can include biosensors which measure the presence of certain biochemical agents (analytes), based on molecular cap-

ture and labelling with magnetic beads. A GMR-type magneto-resistive sensor or other sensor can be used to measure the magnetic stray-field of the bound magnetic beads. From this signal the concentration of the biological agent can be calculated. Such biosensors can be useful for example in point-of-care applications where a low analyte concentration in the sample is to be measured. Analytes can be measured in whole blood, plasma, (filtered) saliva, urine, cell-punctures, etc. Analytes that can be measured are proteins, cells, metabolites, small molecules, electrolytes, antibodies, DNA, RNA, etc.

[0036] Other variation and examples can be envisaged within the scope of the claims.

Claims

1. A fluid handling device for use in analysing a sample fluid, the device having a sample chamber (50, 150) for retaining a predetermined amount of the sample fluid for analysis in the sample chamber, a pre-chamber (20, 130) for retaining the sample fluid before an analysis and having a first vent, an entry (30) to the pre-chamber being arranged to require pressure to inject a fluid sample into the pre-chamber, the device having a connecting passage (40, 140) from the pre-chamber to the sample chamber arranged to allow the predetermined amount of the sample fluid to flow to the sample chamber by capillary action.
2. The fluid handling device of claim 1, wherein the pre-chamber is larger in volume than the fluid sample and the first vent is an air vent.
3. The device of claim 1, wherein the pre-chamber is smaller in volume than the fluid sample and the first vent is a channel to remove excess sample fluid under pressure.
4. The device of claim 3 the connecting passage comprising a micro-channel having sufficiently small cross section and sufficient length for a given viscosity of the sample fluid, to resist the pressure of injection during the sample injection and allow the flow by capillary action.
5. The device of claim 1, wherein the pre-chamber has a capillary uptake channel and the cross-sectional area of the pre-chamber that receives fluid during sample injection is at least 3 times larger than the cross-sectional area of the capillary uptake channel.
6. The device of any of the previous claims, the device being adapted to cooperate with a sensor (70, 170) adjacent to the sample chamber for analysing the sample fluid in the sample chamber.
7. The device of any preceding claim, being formed as

part of a cartridge for inserting into a reader.

8. The device of any preceding claim, the entry to the pre-chamber having a filter (120).
9. The device of any preceding claim, having a receiving surface (110) for a user to press an absorbent material against, to cause the pressure for the injection.
10. The device of claim 9, the receiving surface being conical and above the pre-chamber so as to drain into the pre-chamber.
11. The device of any preceding claim and having a mechanical injector.
12. The device of any preceding claim, the entry having a one way valve.
13. The fluid handling device of any preceding claim, the sample chamber having a second vent (160) to restrict the flow when it reaches the second vent, the second vent being located so as to enable the predetermined amount of the sample fluid into the sample chamber.
14. A system having the fluid handling device of any preceding claim and a reader (60) to which the fluid handling device can be attached to carry out the analysis.
15. A method of preparing a sample of a fluid for analysing, the method having the steps of injecting the fluid into a pre-chamber (20, 130) of a cartridge, the cartridge having a sample chamber (50, 150) for retaining a predetermined amount of the fluid during an analysis, and using a connecting passage (40, 140) from the pre-chamber to the sample chamber to cause the predetermined amount of the fluid to flow to the sample chamber by capillary action.
16. The method of claim 15 having the step of moving the cartridge into a reader (60) for carrying out the analysis.
17. The method of claim 15 or 16 having the step of analyzing the sample in the sample chamber.

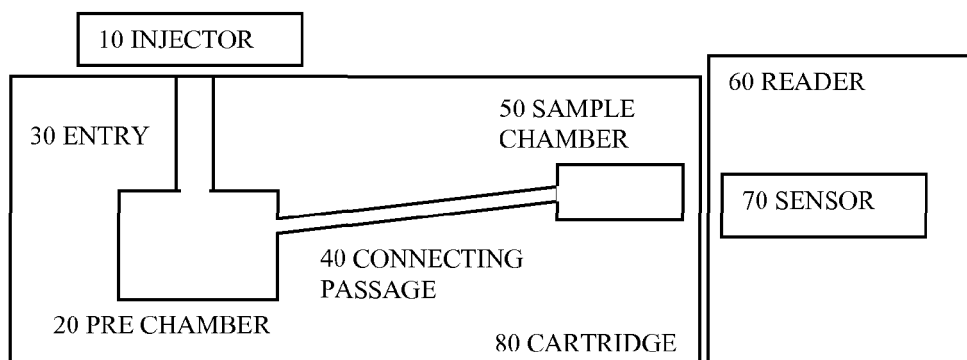


FIG 1

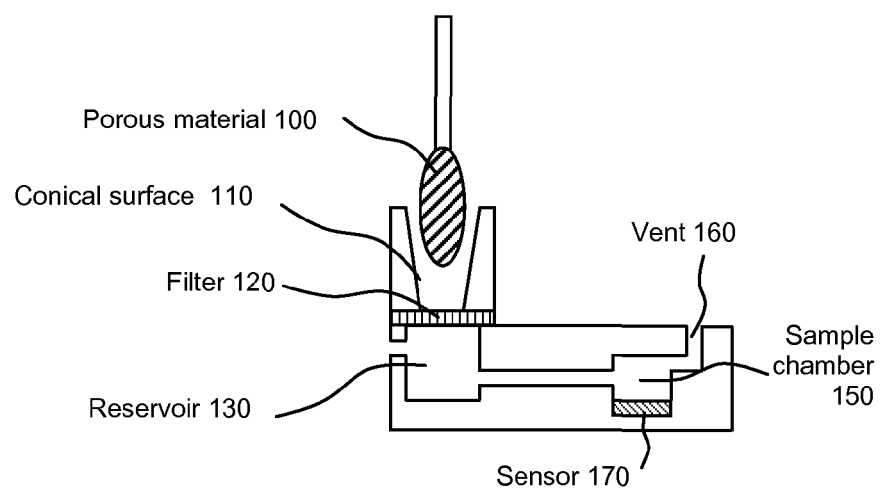


FIG 2

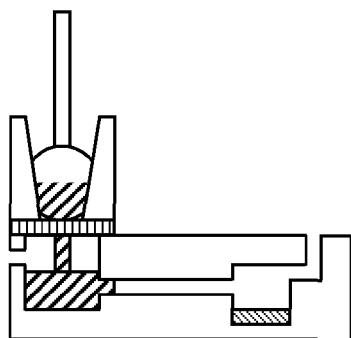


FIG 3

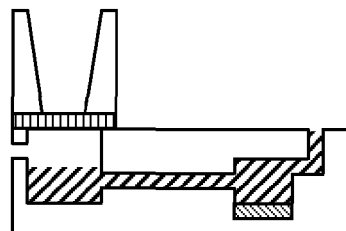


FIG 4

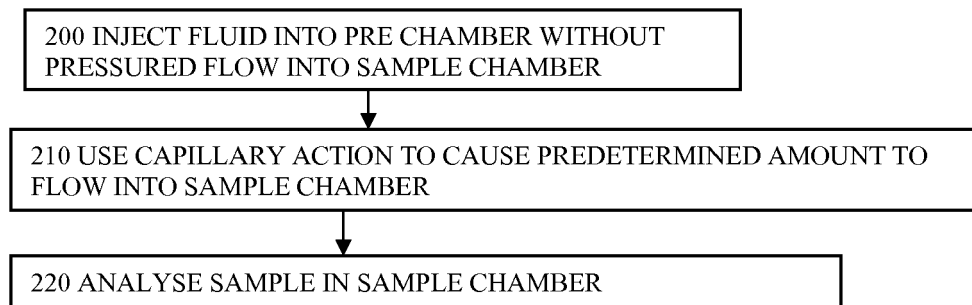


FIG 5



European Patent
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EUROPEAN SEARCH REPORT

Application Number
EP 07 11 8889

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|---|---|---|---|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (IPC) |
| X | US 2004/265171 A1 (PUGIA MICHAEL J [US] ET AL) 30 December 2004 (2004-12-30) * claims 21-24; figure 1 * | 1-17 | INV. B01L3/00 |
| A | EP 0 397 424 A (BIOTRACK INC [US]) 14 November 1990 (1990-11-14) * the whole document * | 1-17 | |
| A | WO 95/06868 A (BOEHRINGER MANNHEIM CORP [US]) 9 March 1995 (1995-03-09) * the whole document * | 1-7 | |
| A | WO 99/41147 A (ROCHE DIAGNOSTICS CORP [US]) 19 August 1999 (1999-08-19) * the whole document * | 1-17 | |
| A | DE 10 2004 063438 A1 (BACKES OKTAVIA [DE]; BACKES PERDITA [DE]) 6 July 2006 (2006-07-06) * the whole document * | 1-17 | |
| | | | TECHNICAL FIELDS SEARCHED (IPC) |
| | | | B01L |
| The present search report has been drawn up for all claims | | | |
| Place of search Munich | | Date of completion of the search 26 March 2008 | Examiner Skowronski, Maik |
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**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 07 11 8889

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26-03-2008

| Patent document cited in search report | | Publication date | Patent family member(s) | | Publication date |
|---|----|---------------------|----------------------------|---------------|---------------------|
| US 2004265171 | A1 | 30-12-2004 | CA | 2529562 A1 | 13-01-2005 |
| | | | EP | 1642112 A2 | 05-04-2006 |
| | | | JP | 2007520692 T | 26-07-2007 |
| | | | WO | 2005003723 A2 | 13-01-2005 |
| ----- | | | | | |
| EP 0397424 | A | 14-11-1990 | AU | 625828 B2 | 16-07-1992 |
| | | | AU | 5475990 A | 08-11-1990 |
| | | | JP | 3067171 A | 22-03-1991 |
| ----- | | | | | |
| WO 9506868 | A | 09-03-1995 | DE | 69433776 D1 | 17-06-2004 |
| | | | DE | 69433776 T2 | 25-05-2005 |
| | | | EP | 0717838 A1 | 26-06-1996 |
| | | | ES | 2220914 T3 | 16-12-2004 |
| | | | JP | 3470973 B2 | 25-11-2003 |
| | | | JP | 9502521 T | 11-03-1997 |
| ----- | | | | | |
| WO 9941147 | A | 19-08-1999 | AU | 3288799 A | 30-08-1999 |
| | | | CA | 2320053 A1 | 19-08-1999 |
| | | | DE | 69931469 T2 | 22-02-2007 |
| | | | EP | 1054805 A1 | 29-11-2000 |
| | | | ES | 2264262 T3 | 16-12-2006 |
| | | | JP | 3589980 B2 | 17-11-2004 |
| | | | JP | 2002502681 T | 29-01-2002 |
| | | | US | 5975153 A | 02-11-1999 |
| ----- | | | | | |
| DE 102004063438 | A1 | 06-07-2006 | AU | 2005321534 A1 | 06-07-2006 |
| | | | CA | 2592085 A1 | 06-07-2006 |
| | | | EP | 1846160 A1 | 24-10-2007 |
| | | | WO | 2006069757 A1 | 06-07-2006 |
| ----- | | | | | |

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- EP 1285628 A [0002]
- US 6926225 B [0003]
- US 5096669 A [0004]