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(71) Applicant: **Coris Bioconcept SPRL**
5032 Gembloux (BE)

(72) Inventors:
- **Mertens, Pascal**
  5340 Haltinne (BE)
- **Ote, Isabelle**
  4000 Liège (BE)
- **Leclipteux, Thierry**
  5100 Wépion (BE)
- **Aussems, Eric**
  3793 Fourons (BE)

(74) Representative: **Pronovem**
Office Van Malderen
Avenue Josse Goffin 158
1082 Bruxelles (BE)

(54) DISPOSABLE FLOW CHIP DEVICE

(57) The present invention is related to a disposable flow chip device (1) comprising a microfluidic chip (2) comprising two reservoirs (13, 14) being in fluidic communication with a micro-channel (18), with one or more detection zone(s) (23) and with connectors (12), a pump cartridge (3) comprising a pipe (9) being in contact, in use, with one or more roller(s) (27) of an external peristaltic pump (4), and hermetic connectors (10) complementary to the microfluidic chip connectors (12), wherein the pipe (9) is in fluid communication with the reservoirs (13, 14) of the microfluidic chip (2). The invention relates also to a method and an apparatus for detecting and/or quantifying one or more analyte(s) possibly present in a biological sample using the disposable flow chip device (1) according to the invention.

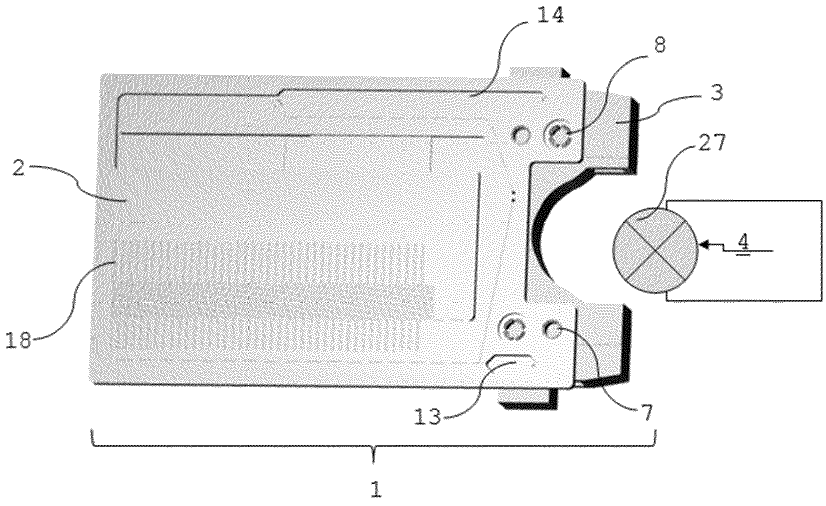

FIG. 1

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Description

Field of the Invention

[0001] The present invention relates to an improved method and device for a genetic amplification and/or a rapid detection of an analyte, possibly present in a fluid sample, especially to a disposable flow chip device, comprising a chip for carrying a microfluidic assay and an interface which is capable, in use, to be easily connected to an external pumping system. The invention is also related to an apparatus comprising the external pumping system.

State of the Art

[0002] Lab-on-chip which is able to automatically operate a biological sample processing has been developed in many countries in the world. In these chips, the microfluidic driving system that drives a fluid that contains samples of biochemical agents, DNAs or proteins for example, inside microfluidic channels is one of the most important equipment. The question of how to easily control fluid movement and avoid the cross contamination of the sample or the biochemical agents with the driving system, has become a question of interest.

[0003] Microfluidic driving systems that are known to the public may be divided into three classes: on-chip mechanical micro-pumps, on-chip electro kinetic micro-pumps and pump systems which are external to the chip.

[0004] On-chip mechanical micro-pumps present the drawback of being embedded mechanical micro-pumps prepared directly in a chip with the micromachining technology. Generally, such devices comprise moveable parts in the chip and comprise a pressure chamber. An intermittent electrostatic driving force is generated between the two-layer structure of the pressure chamber and the two one-way passive check valves positioned in the microfluidic channel are driven in turn. Such an operation generates a pumping force to the fluid.

[0005] U.S. Pat. No. 5,705,018 discloses a micro peristaltic pump, wherein a series of flexible conductive strips are provided along the inner wall of the micro-channel provided in the chip. When voltage pulses pass over the micro-channel, the flexible conductive strips are pulled upward by electrostatic force generated in turn. A peristaltic phenomenon takes thus place. The fluid in the micro-channel is driven by the driving force of the strips.

[0006] In such a mechanical microfluidic driving system provided with moveable elements and with a complicated structure, it is very difficult to clean up all residuals of samples or biochemical reagents of another experiment. As a result, most microfluidic driving systems for the chips shall be disposable. However, both the embedded rotational micro-pump and the embedded peristaltic micro-pump have complicated process of manufacture and expensive customer design components, which make the preparation costs of the micro-pump relatively high and moreover the micro-pump is not reusable. Such a micro-pump is not suited in disposable chips.

[0007] In addition to that, the mechanical micro-pumps are generally prepared with membranes, valves or gears which are driven by relatively higher powers, such as electric, magnetic or thermal powers. Such a requirement involves complicated structure, complicated operations and higher costs. Furthermore, it is even more difficult to prepare a pump or pump module that provides driving forces back and forth in the micro-channel.

[0008] On-chip electro kinetic micro-pumps are non-mechanical micro-pumps. Inside the pumps, there are no moveable elements. Operations of such a micro-pump may be carried out by electro-osmosis, electro-hydrodynamic or electrophoresis.

[0009] U.S. Pat. No. 5,632,876 discloses an apparatus and methods for controlling fluid flow in micro-channels employing the combination of the electro-osmosis power and the electro-hydrodynamic power. The apparatus comprises a micro-channel provided in a chip and two pairs of electrodes, four in total, are arranged in the micro-channel in turn. A pair of electrodes is deeply put in the micro-channel. When high voltage is applied to the electrodes, fluid adjacent to the electrodes will be carried in a direction reverse to the direction of the electrical current. An electro-hydrodynamic pumping is thus accomplished.

[0010] An electrode micro-pump is simple in structure, low in manufacture cost but limited in application. First, inside the micro-channel, solvent must be filled before anything may be driven. It is not possible to introduce samples or reagents into empty channels. Secondly, the distance over which an electro-hydrodynamic pump can drive a fluid is limited. The electro-hydrodynamic pump can only be applied to nonpolar organic solvents, while the electro-osmosis pump and the electrophoresis pump can only be applied to polar solvents. The driving efficiency of the pumps is highly influenced by the concentration of ions in the solution. When the ion concentration of the solution varies during the reaction, the driving of the solution will become more difficult to control.

[0011] In pump systems wherein the pump is external to the chip, there is no need to provide any active element in the chip containing the micro-channel to drive the fluid. Such a chip is easily prepared under a lower cost. The pump system external to the chip is not directly connected to the samples or the reagents and may be used repeatedly and possibly simultaneously upon numerous chips. This type of external pump is connected to the chip through an interface.

[0012] WO 2014/005969 discloses a flow chip wherein a dynamic constant flow in a closed circuit is applied using an external peristaltic pump or roller pump. The chip comprises two reservoirs, one containing the sample and the other containing a migration buffer. After the introduction of the fluids into the chip, the two reservoirs are connected by a flexible tube forming a loop and adapted to come into contact with one or more rollers of a peristaltic pump.

This tube is the interface such that its contact with rollers of the peristaltic pump ensures constant flow dynamics of the sample and buffer in the channel of the flow chip.

[0013] One problem of the device disclosed in WO 2014/005969 is the interface between the pump and the chip. The use of a flexible tube presents several drawbacks having an impact on the flow dynamics within the chip, drawbacks such as the difficulties encountered by the end user to connect the chip and the pump. Furthermore, in such device, the sample and its analyte can be contaminated by the environment or may comprise gas (air) introduced while introducing the sample in the device, leading to unwanted and possibly harmful internal pressure increase.

[0014] Therefore, there is a need to improve the interface between a disposable flow chip and its external pumping system.

Aims of the Invention

[0015] The present invention aims to provide a method and a disposable flow chip device that do not have the drawbacks of the prior art. It particularly aims to provide a flow chip device remaining hermetically closed after the introduction of the fluid sample(s) and allowing gas or air release, which are possibly present in the microfluidic elements of the flow chips before introduction of the fluid sample(s), and therefore avoiding or reducing any interference in the fluids flow inside the device. Another aim of the invention is to propose a suitable interface for connecting efficiently this flow chip device to an external pump.

Summary of the Invention

[0016] The present invention discloses a disposable flow chip device comprising a microfluidic chip comprising two or more reservoirs being in fluidic communication with a micro-channel, with one or more detection zone(s) and with connectors, preferably luers, a pump cartridge comprising a pipe being in contact, in use, with one or more roller(s) of an external peristaltic pump, and hermetic connectors, preferably luer connectors, complementary to the microfluidic chip connectors, wherein the pipe is in fluid communication with the reservoirs of the microfluidic chip.

[0017] The specific embodiments of the invention include at least one of, or a suitable combination of, the following features:

- the pipe of the pump cartridge is in fluid communication with the reservoirs of the microfluidic chip by means of connectors, especially luer connectors, connecting hermetically each end of the pipe to connectors (luers) of the microfluidic chip,
- the reservoirs are connected by means of venting channels to venting holes in the microfluidic chip,
- the venting holes are sealed by a lid,
- the pump cartridge comprises at least two pins plugged into complementary holes of the microfluidic chip,
- the pin is a snap fit pin,
- the pipe of the pump cartridge is made of a material selected from the group consisting of silicone or ethylene-propylene-diene monomer (EPDM),
- the microfluidic chip comprises a micro-channel having a diameter comprised between 10 μm and 900 μm, a sheet-like chromatographic device in fluidic communication with the micro-channel, the chromatographic device comprising an application region, one or more detection region(s), wherein the detection region comprises at least one capture reagent specifically recognizing a labelled polynucleotide sequence or a labelled polypeptide to generate a specific signal,
- the micro-channel comprises multiple loops crossing at least two, preferably three, different temperature zones, each zone having a constant temperature and wherein said loops are configured for multiple amplification cycles of a PCR.

[0018] The present invention further discloses a method to detect and/or quantify one or more analyte(s) possibly present in a biological sample, the method comprising the steps of providing the disposable flow chip device according to the invention, providing one or more analyte(s) comprising a target polynucleotide sequence or polypeptide specific of the said analyte(s), filling the reservoir of the disposable flow chip device with the one or more analyte(s) and submitting the one or more analyte(s) to a fluid flow within the disposable flow chip device.

[0019] The present invention further discloses an apparatus to detect and/or quantify one or more analyte(s) possibly present in a biological sample, the apparatus comprising one or more disposable flow chip device(s) according to the invention, a holder for holding the disposable flow chip device(s), a peristaltic pump comprising multiple rollers intended to contact the pipe of the pump cartridge, a heating device providing different temperature zones to the disposable flow chip device, a detector for measuring a signal generated on the disposable flow chip device.

[0020] The present invention will be described in detail in the following description in reference to the enclosed figures presented as non-limiting embodiments of the present invention.

Brief Description of the Drawings

[0021]

Fig. 1 is representing a bottom view in perspective of a disposable flow chip device of the invention.

Fig. 2 is representing a top view in perspective of the disposable flow chip device of figure 1.

Fig. 3A is representing a bottom perspective view of the pump cartridge being part of the disposable flow chip device of the invention.

Fig. 3B is representing a perspective view of the pump cartridge without the pump pipe and the fluid connectors.

Fig. 3C is representing a cross section view of the pump pipe and fluid connectors that are present in the pump cartridge.

Fig. 4A, 4B and 4C represent different microfluidic designs being part of the disposable flow chip device of figure 1.

Detailed Description of the Invention

[0022] An example of the disposable flow chip device 1 according to the invention is represented in figure 1 (bottom view) and figure 2 (top view). It comprises two parts, a microfluidic chip 2 and a pump cartridge 3, which are assembled by connection means, preferably connectors, more preferably connectors hermetic to fluids and/or gas or air, for example luers 12 and luer connectors 10. The disposable flow chip device 1 is thus hermetically closed when these two parts are assembled. Furthermore, having hermetic connectors 10 and 12 presents the advantage of reducing or eliminating the sample contamination risks during the use of the device.

[0023] The pump cartridge 3 comprises a pipe 9 (visible in figure 3A) intended to be, in use, in contact with one or more roller(s) 27 of an external peristaltic pump 4. Therefore, the pipe 9 is in fluid communication with the reservoirs 13 and 14 of the microfluidic chip 2 so that, when the external pump 4 is running, the fluid can flow through the pipe 9 (i.e. through contact between the rollers applied upon the pipe 9) in a continuous manner between the chip 2 and the pump cartridge 3, by means of the action of the rollers of the external pump on the (flexible) pipe 9.

[0024] Having the pipe 9 being part of the pump cartridge 3 avoid the problem encountered by the end user to connect the chip and the pump, leading to a device more easy to use.

[0025] Preferably, the pipe 9 is a tubing, more preferably a flexible tubing.

[0026] Preferably, the pump cartridge 3 has a U shape comprising a bridge section and two legs interconnected by the bridge section. In this embodiment, the pipe 9 is preferably provided in the plan formed by the pump cartridge 3, from one leg to the other. Preferably, the pump cartridge 3 is assembled, connected, to the microfluidic chip 2 by means of the bridge section.

[0027] As shown in figure 3B, the pump cartridge 3 preferably comprises one or more pins 7 for plugging the pump cartridge 3 into the microfluidic chip 2 which have complementary holes, or recess, 15, 16, having a size and a shape suitable to receive said pins 7.

[0028] The pump cartridge 3 preferably comprises one or more cavities 5 suitable to receive one or more connectors, for example luer connectors 10, and at least one cavity 6 suitable to receive a lid 11.

[0029] The connectors 10 are, in shape and size, complementary to the microfluidic chip connectors 12 (visible on figures 4A, B and C) and allow hermetic connection between the pump cartridge 3 to the microfluidic chip 2. The venting holes 17 present on the microfluidic chip 2 (visible on figures 4A, B and C) allow a gas, for example air, to be released from the microfluidic elements of the microfluidic chip when the reservoirs 13, 14 are filled, allowing thus a better filling of the reservoirs 13 and 14 and also allowing a more constant flow of the fluid within the channel of the chip. Preferably, in the assembled disposable flow chip device of the invention, the venting holes 17 are hermetically closed by a lid 11 provided on the pump cartridge 3 allowing to have a device hermetically closed and less subject to contaminations.

[0030] A cross section view of the pump pipe 9 and the connectors 10 is shown in figure 3C.

[0031] Figures 4A, 4B and 4C represent different embodiments of the microfluidic chip 2.

[0032] In a first embodiment (figure 4A), the microfluidic chip 2 is suitable for amplification and rapid detection of target nucleotide sequences possibly present in a sample. It may combine continuous-flow genetic amplification (PCR) with oligo-chromatography detection by capillary action on a test strip. In this embodiment, the chip 2 comprises a first part comprising means for the genetic amplification of nucleic acid sequences specific of an analyte to be detected and possibly present in a fluid sample, submitted thereafter to constant dynamic fluid flow therein, combined with a second part comprising means for the detection of the amplified nucleic acid sequences on a (one or more) sheet-like chromatographic test strip 26 (being in fluidic communication with the channel 18) and allowing thereafter an identification of the corresponding analyte present in the sample submitted to analysis. The two parts are in fluidic communication by means of a connection channel 19.

[0033] The first part of the microfluidic chip 2 is suitable for genetic amplification (PCR) of one or more target sequence(s) to be detected. It comprises a micro-channel 18 (having a section comprised between about 10 μm and about 900 μm) in a serpentine configuration comprising a plurality of loops capable of performing different steps of the genetic amplification process, these loops being in contact, in use, with an external heating means at different zones (or areas) of the loops, preferably two, more preferably three different temperature zones, each zone having a constant temperature. Preferably, heating means consist of Peltier devices or heating resistances or heating blocks in aluminium and adequate sensors. The micro-channel 18 has a coil configuration, a length and dimensions that may vary, but comprises a certain number of loops able to carry out the different steps required for a suitable genetic amplification (by PCR).

[0034] The second part of the microfluidic chip 2 comprises a sheet-like chromatographic strip 26 incorporat-

ing three zones or regions. These three zones consist of one or more porous membranes allowing the migration by capillary action of a fluid and its components, i.e. the solution comprising the amplified sequences, from a proximal region 20 to a distal region 21. The three zones comprise an application region 22, a detection region 23 and an absorption region 24.

[0035] Preferably, the membrane of the application zone 22 comprises or consists of glass fibres or polyester, the membrane of the detection zone 23 comprises or consists of nitrocellulose and the absorption region 24 comprises or consists of cellulose. Other structures and materials used by a skilled person in the art to improve migration by capillary action in the chromatographic strip 26 or to improve the integration of elements used for the detection on the strip are possible.

[0036] Preferably, the microfluidic chip 2 is made of a material selected from the group consisting of glass, quartz or plastic, in particular in polycarbonate or in cyclo olefin polymer, and is obtained by injection molding. The microstructures of the micro-channel are preferably performed by photolithography. The aperture of the micro-channel 18 is optionally adapted for facilitating introduction and preliminary treatment of the sample to be tested and optionally diluted.

[0037] In a second embodiment (figure 4B), the microfluidic chip 2 is suitable for the amplification and rapid detection of target nucleotide sequences specific of the analyte present in the fluid sample. It combines continuous-flow genetic amplification (PCR) with oligo-chromatography detection by capillary action on two or more (separated) test strips for multiplexing the number of target nucleotide sequences detected simultaneously and thus for multiplexing the identification of analytes potentially simultaneously present in the fluid sample submitted to analysis.

[0038] In a third embodiment (figure 4C), the microfluidic chip 2 is suitable for the rapid detection of a target analyte, for example any biological analyte, such as an antigenic structure to be detected by immunochromatography, possibly present in a fluid sample without previous genetic amplification (PCR). It combines continuous-flow of a sample solution with immunochromatography detection by capillary action on a test strip.

[0039] The principle of the analysis of a biological sample is the following. The reservoir 13 of the microfluidic chip 2 is filled with a fluid sample reagent and the reservoir 14 is filled with a buffer. During this filling process, the gas, i.e. air, which is displaced by the fluids, the liquid samples, is escaping, released outside the device, via the venting channels 25 to the venting holes 17.

[0040] The pump cartridge 3 is manually or mechanically plugged into the microfluidic chip 2 by means of complementary connectors 10 and 12. The pump cartridge 3 comprises pins 7 and/or snap fit pins 8 that are complementary to holes 15 and 16 present in proximity of the connectors 12 of the microfluidic chip 2. When the pump cartridge 3 is positioned over the microfluidic chip 2, and that the pins and snap fit pins 7 and 8 are pressed into their complementary holes, these pins 7 and 8 clamp the pump cartridge 3 against the microfluidic chip 2. This action also clamps the hermetic connectors 10 into the connectors 12 of the microfluidic chip 2, and closes the venting holes 17 by the adequate presence of the lid 11. In the assembled device, the pipe 9 of the pump cartridge 3 is thus in fluid communication with the reservoirs 13 and 14 of the microfluidic chip 2, and the whole microfluidic circuit is hermetically closed.

[0041] The assembled disposable flow chip device of the invention is ready for activation of the fluids to detect and/or quantify one or more analyte(s) present in a biological sample. The pipe 9 of the pump cartridge 3 is brought into contact with one or more roller(s) 27 of the external peristaltic pump 4 in the analyzer. The sample reagent is pumped into the micro-channel 18 and is processed by continuous dynamic flow until it is detected in the detection zone 23 of the microfluidic chip 2.

Numeral references of the drawings

[0042]

1. Disposable flow chip device
2. Microfluidic chip
3. Pump cartridge
4. Peristaltic pump with rollers
5. Cavity for the pump pipe connector 10
6. Cavity for the venting holes lid 11
7. Pin
8. Snap fit pin
9. Pump pipe
10. Pump pipe connector
11. Venting holes lid
12. Connector complementary to the pump pipe connector 10
13. Sample reservoir
14. Buffer reservoir
15. Hole complementary to the pin
16. Hole complementary to the snap fit pin
17. Venting holes
18. Micro-channel
19. Connection channel
20. Proximal region
21. Distal region
22. Application region
23. Detection region
24. Absorption region
25. Venting channel
26. Sheet-like chromatographic strip
27. Pump rollers

Claims

1. Disposable flow chip device (1) comprising:

- a microfluidic chip (2) comprising two reservoirs (13, 14) being in fluidic communication with a micro-channel (18), with one or more detection zone(s) (23) and with connectors (12);
- a pump cartridge (3) comprising a pipe (9) being in contact, in use, with one or more roller(s) (27) of an external peristaltic pump (4), and hermetic connectors (10) complementary to the microfluidic chip connectors (12); and wherein said pipe (9) is in fluid communication with the reservoirs (13, 14) of the microfluidic chip (2).

2. The disposable flow chip device (1) of claim 1, wherein the pipe (9) of the pump cartridge (3) is in fluid communication with the reservoirs (13, 14) of the microfluidic chip (2) by means of hermetic connectors (10) which connect hermetically each end of the pipe (9) to connectors (12) of the microfluidic chip (2).

3. The disposable flow chip of claim 1 or 2, wherein the microfluidic chip connectors (12) are luers.

4. The disposable flow chip device (1) according to any of the preceding claims, wherein the reservoirs (13, 14) are connected by means of venting channels (25) to venting holes (17) in the microfluidic chip (2).

5. The disposable flow chip device (1) of claim 4, wherein the venting holes (17) are hermetically sealed by a lid (11).

6. The disposable flow chip device (1) of any of the preceding claims, wherein the pump cartridge (3) is manually or mechanically plugged into the microfluidic chip (2) by means of complementary connectors (7, 8, 15, and 16).

7. The disposable flow chip device (1) of claim 6, wherein the pump cartridge (3) comprises at least two pins (7, 8) plugged into complementary holes (15, 16) of the microfluidic chip (2).

8. The disposable flow chip device (1) of claim 7, wherein the pin is a snap fit pin (8).

9. The disposable flow chip device (1) of any one of the preceding claims, wherein the pipe (9) of the pump cartridge (3) is made of a material selected from the group consisting of silicone or ethylene-propylene-diene monomer (EPDM).

10. The disposable flow chip device (1) of any one of the preceding claims, wherein the microfluidic chip (2) comprises:

- a micro-channel (18) having a diameter comprised between 10 μm and 900 μm;
- a sheet-like chromatographic device (26) in fluidic communication with said micro-channel (18), said chromatographic device (26) comprising an application region (22), one or more detection region(s) (23), wherein said detection region (23) comprises at least one capture reagent specifically recognizing a labelled polynucleotide sequence or a labelled polypeptide to generate a specific signal.

11. The disposable flow chip device (1) of claim 10, wherein the micro-channel (18) comprises multiple loops crossing at least two different temperature zones, each zone having a constant temperature and wherein said loops are configured for multiple amplification cycles of a PCR.

12. The disposable flow chip device (1) of claim 11, wherein the micro-channel (18) comprises multiple loops crossing three different temperature zones.

13. A method to detect and/or quantify one or more analyte(s) possibly present in a biological sample, the method comprising the steps of:

- providing the disposable flow chip device (1) according to any of the claims 1 to 12,
- providing one or more analyte(s) comprising a target polynucleotide sequence or polypeptide specific of the said analyte(s),
- filling the reservoir (13) of said disposable flow chip device (1) with said one or more analyte(s),
- submitting said one or more analyte(s) to a fluid flow within said disposable flow chip device (1).

14. An apparatus to detect and/or quantify one or more analyte(s) possibly present in a biological sample comprising:

- one or more disposable flow chip device(s) (1) according to any of the claims 1 to 12;
- a holder for holding said one or more disposable flow chip device(s) (1);
- a peristaltic pump (4) comprising multiple rollers (27) intended to contact the pipe (9) of the pump cartridge (3);
- a heating device providing different temperature zones to the disposable flow chip device (1);
- a detector for measuring a signal generated on the disposable flow chip device (1).

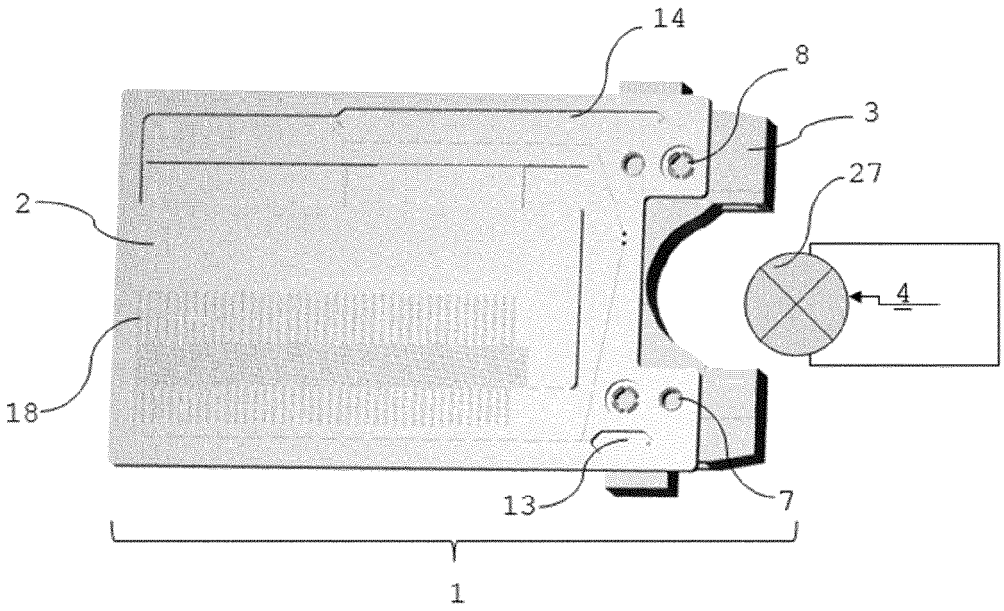

FIG. 1

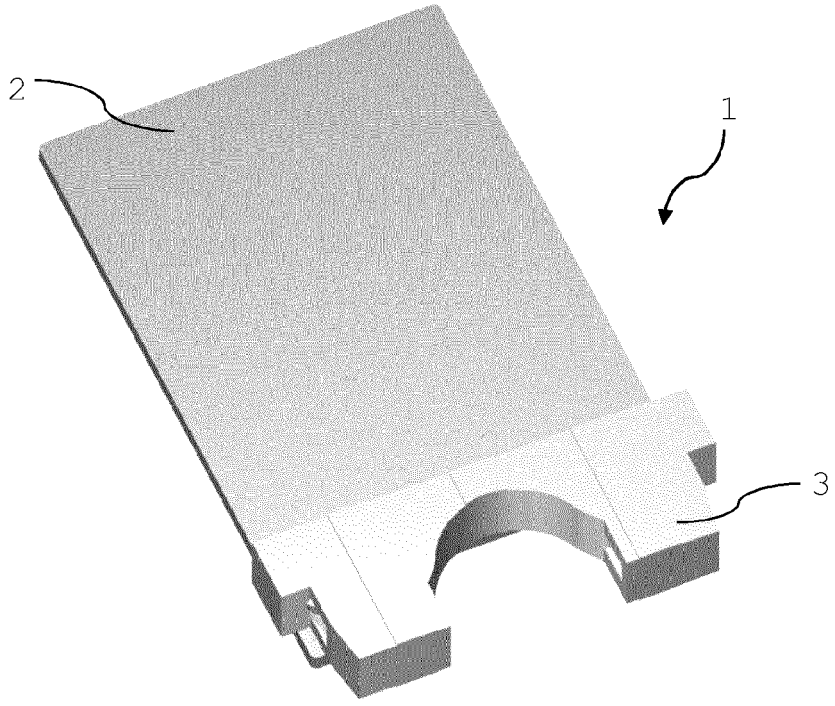

FIG. 2

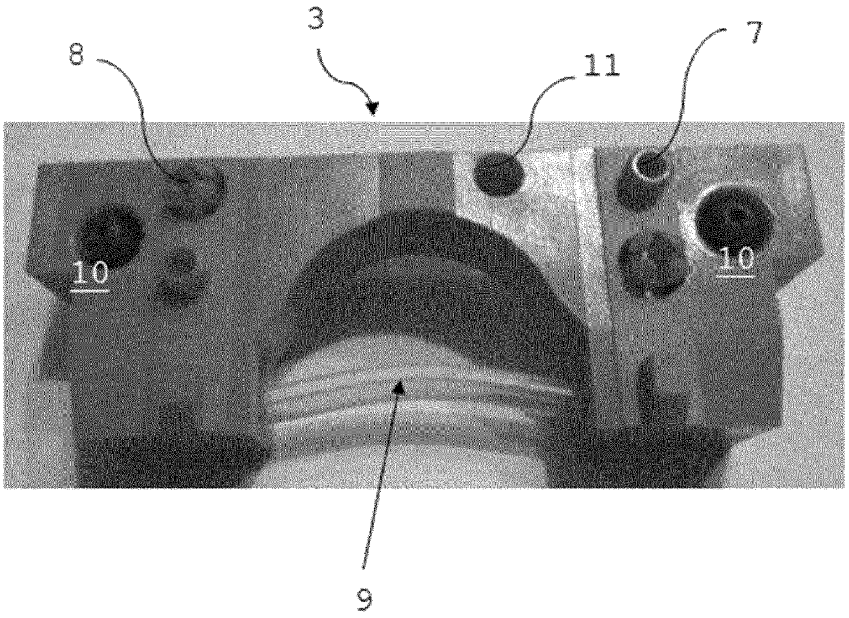

FIG. 3A

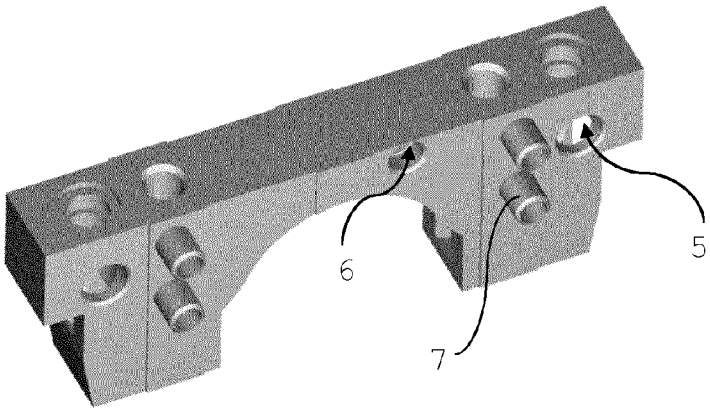

FIG. 3B

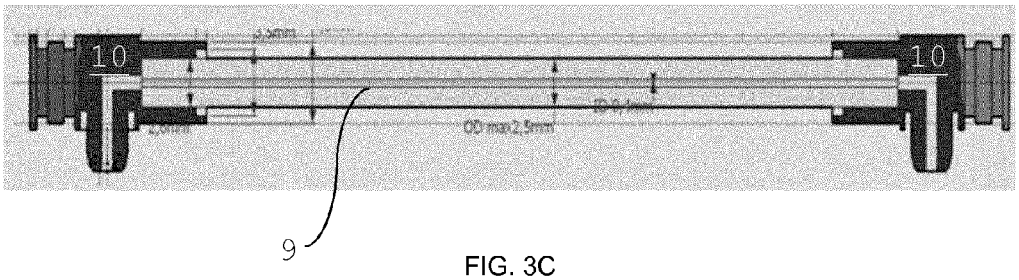

FIG. 3C

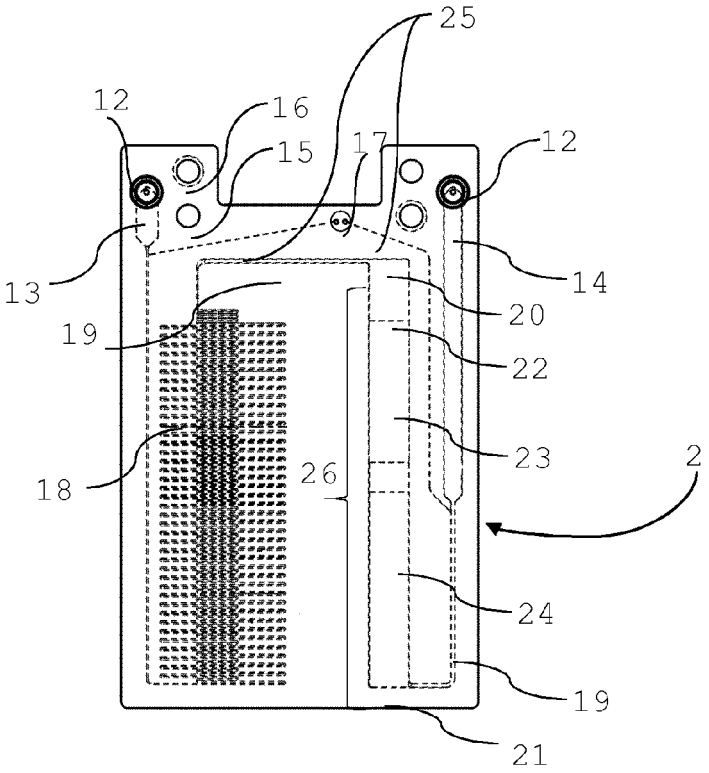

FIG. 4A

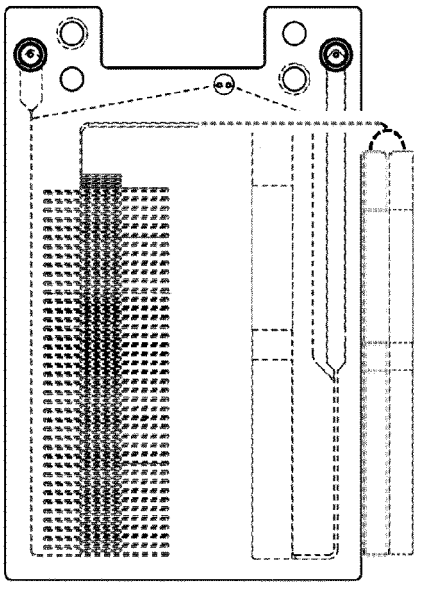

FIG. 4B

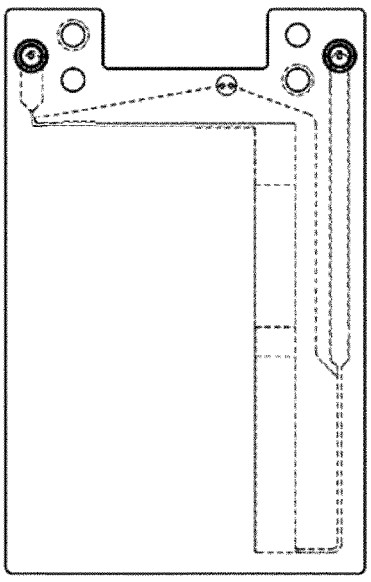

FIG. 4C

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EUROPEAN SEARCH REPORT

Application Number
EP 15 16 2040

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	FR 2 672 301 A1 (LARZUL DANIEL [FR]; EIBET [FR]) 7 August 1992 (1992-08-07) * abstract * * page 10, line 2 - page 15, line 16 * * page 19, line 33 - page 22, line 32 * * figures 1-5,10 *	1-14	INV. B01L3/00
A,D	WO 2014/005969 A1 (CORIS BIOCONCEPT SPRL [BE]) 9 January 2014 (2014-01-09) * the whole document *	1-14	
A	EP 2 290 354 A1 (HACH LANGE GMBH [DE]) 2 March 2011 (2011-03-02) * the whole document *	1-14	
A	US 2004/101444 A1 (SOMMERS JEFF [US] ET AL) 27 May 2004 (2004-05-27) * the whole document *	1-14	
			TECHNICAL FIELDS SEARCHED (IPC) B01L

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	16 September 2015	Sinn, Cornelia

CATEGORY OF CITED DOCUMENTS

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 15 16 2040

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