



(51) International Patent Classification:

F04B 19/00 (2006.01)

F04B 43/06 (2006.01)

F04B 43/02 (2006.01)

(21) International Application Number:

PCT/NL2021/050639

(22) International Filing Date:

21 October 2021 (21.10.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2026780

27 October 2020 (27.10.2020)

NL

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(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO,

DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN,

KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD,

ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO,

NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,
SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH,

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ,

TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,

MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

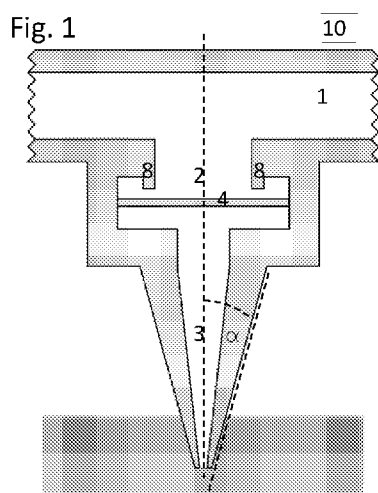
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,

KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: Precise fluid manipulation in the femtolitre range



(57) Abstract: The present invention relates to a microneedle (10) for precise fluid manipulation in the femtolitre range, and a method for fluid manipulation comprising using the microneedle (10). Micropumps, and likewise microneedles, are devices that can control and manipulate small fluid volumes, with functional dimensions in the micrometer range, and hence volumes in or above the picolitre range.



Precise fluid manipulation in the femtolitre range

FIELD OF THE INVENTION

5 The present invention relates to a microneedle for precise fluid manipulation in the femtolitre range, and a method for fluid manipulation comprising using the microneedle. Micropumps, and likewise microneedles, are devices that can control and manipulate small fluid volumes, with functional dimensions in the micrometer range, and hence volumes in or above the picolitre range.

BACKGROUND OF THE INVENTION

10 The present invention is in the field of microfluidic devices, such as micropumps and microneedles, for precise fluid manipulation, and methods for fluid manipulation. Micropumps, and likewise microneedles, are devices that can control and manipulate small fluid volumes, with functional dimensions in the micrometer range, and hence volumes in or above the picolitre range. Micropumps are devices that can control and manipulate small
15 fluid volumes. Although any kind of small pump may be referred to as micropump, typically pumps with functional dimensions in the micrometer range are considered. Such pumps may be of special interest in microfluidic research, and are available for industrial product integration in recent years.

One of the challenges when performing experiments with single cells in vitro is the
20 precise manipulation of liquids in the sub-picolitre range of volumes. Particularly, there is a need to inject or extract very small amounts of fluids from the cell in a controlled manner. Examples of existing micro-tools for this purpose rely on microneedles attached to a microfluidic channel, where the extraction (injection) of fluid is enabled by applying short pulses of underpressure (overpressure) in the microfluidic channel. Although this method has
25 demonstrated the manipulation of very small volumes, the exact dose of extracted/injected liquid is not easily controllable, and the reproducibility is poor. The other major challenge of the existing method is the dilution of the extracted sub-volume with the liquid in the microneedle channel due to diffusion. Similarly, the liquid in the micro-needle will be diluted near the tip due to diffusion during injection.

30 US 5,759,014 (A) provides an example of a micropump, comprising two glass wafers with a machined silicon wafer sealingly inserted therebetween. An inlet valve, a pump chamber and an outlet valve are arranged between an inlet channel and an outlet channel. A pump diaphragm forming one wall of the pump chamber comprises a thicker central portion operating like a piston. A piezoelectric element acts on the diaphragm via an intermediate
35 part to provide the pumping movement. The pump chamber and the spaces linking the pump chamber to the inlet and outlet valves are shaped so that the reduction in the inner volume of the micropump caused by a reduction in the volume of the pump chamber during the pumping movement is such that the air in the micropump is compressed to a pressure high enough to open the outlet valve, whereby the micropump is self-priming.

US 6,280,148 B1 recites a microdosing device comprising a pressure chamber which is at least partly delimited by a displacer, an actuating device for actuating the displacer, the volume of the pressure chamber being adapted to be changed by actuating the displacer, a media reservoir which is in fluid communication with the pressure chamber via a first fluid line, and an outlet opening which is in fluid communication with the pressure chamber via a second fluid line. The microdosing device additionally comprises a means for detecting the respective position of the displacer and a control means which is connected to the actuating device and to the means for detecting the position of the displacer, said control means controlling the actuating device on the basis of the detected position of the displacer or on the basis of displacer positions detected during at least one preceding dosing cycle so as to cause the discharge of a defined volume of fluid from the outlet opening.

The prior art devices do not provide very precise dosing and control of very small volumes, such as femtolitre dosing. The devices are also typically dedicated to either dispensing or aspirating. The above devices are also rather complex. Combination with these prior art devices and a further device, such as an electron or atomic force microscope, is difficult if not impossible. The latter is in particular the case when dealing with cells, such as with single cells.

Some prior art devices relate to relatively complex structures. For instance, US 2011/172639 (A1) recites a device for delivering a drug into the skin of a subject is provided. The device includes a drug reservoir and a microneedle having a tip, a length, and a tip sharpness. The microneedle is coupled to the reservoir. The device includes a microneedle actuator coupled to the microneedle configured to drive the microneedle into the skin of the subject upon activation. The tip sharpness and the actuator allow the microneedle to pass through an outer layer of the skin upon activation, and the length is limited such that the tip does not extend past a desired depth below the surface of the skin of the subject, wherein the desired depth is located in the papillary dermis or the reticular dermis. US 2014/377091 (A1) recites a pump devoid of mobile mechanical parts and including a tank with a sleeve for dispensing fluid that remains fully open, but of which an inside capillary is too thin to allow for dispensing of fluid when idle. Recourse is therefore made to a resonator device with a piezoelectric exciter, that produces vibrations, in particular bending, of the sleeve to oblige the fluid to flow through it at a determined flow rate that depends on characteristics of the pump and of excitation. The assembly can be miniaturized and used as an implantable device, for example for treatment of hearing pathologies, to deliver a drug, or, in certain embodiments, also take samples of ambient fluid. A remote energy supply is possible.

The present invention therefore relates to a device for precise fluid manipulation in the femtolitre range and further aspects thereof, which overcomes one or more of the above disadvantages, without compromising functionality and advantages.

SUMMARY OF THE INVENTION

It is an object of the invention to overcome one or more limitations of the micronee-

dles of the prior art and at the very least to provide an alternative thereto. The present invention relates to a new type of microneedle that incorporates a membrane in the path between the needle tip and the microfluidic channel (see e.g. Fig. 1). This membrane prevents the free flow of the liquid into the microfluidic channel. At the same time, the membrane is able to
5 deform as a result of the pressure applied in the microfluidic channel, changing the volume of the needle cavity to allow liquid in or out. A fine control of the exact volume of liquid manipulated is achieved by the elastic deformation of the membrane, that for instance may follow a linear relation with the applied pressure. The deformation of the membrane is typically limited by the upper boundaries of the present chamber, and therewith an exact volume
10 is defined. In addition any underpressure, being sufficient to deform the membrane accordingly, may then be applied, and not much control of the pressure is required, if any. The rigidity of the membrane and its maximum linear deformation are tailored by selection of material and dimensions. In experiments involving extracting biological material from living cells or other biological entities, the needle cavity is typically prefilled with a buffer solution
15 to ensure the viability of the material. An air hole may be incorporated in the membrane to allow the evacuation of the air in the needle cavity and its replacement with buffer solution (see Fig. 4b). The surface tension of the buffer/air interface is considered to prevent the flow of the buffer solution through the air hole. The small volume of buffer contained in the needle cavity limits the diffusion of the extracted material, as opposed to existing devices in
20 which the large-volume microchannel has to be completely filled with buffer. In a first aspect the present invention relates to a microneedle 10 comprising a chamber 2 for providing a fluid, a fluid channel 1, the fluid channel in fluid connection with an upper part of the chamber, and a needle tip 3 in fluid connection with a lower part of the chamber, wherein the chamber comprises a membrane 4, wherein the membrane extends fully over the fluid con-
25 nection of the chamber and prevents liquid flow from a lower part of the chamber to the upper part of the chamber, and vice versa. With this simple set-up precise dosing and control thereof is achieved. The chamber may be considered a central part of the microneedle, which is in fluidic contact with the fluid channel at a first side thereof and with the needle tip at another side thereof, typically opposite sides, such as bottom/to or left/right, wherein these
30 sides are of course relative to an orientation of the microneedle itself. In the chamber a membrane is provided. The membrane is used to create an over-pressure or under-pressure, respectively, for dispensing or aspirating a fluid out of or into the microneedle. The membrane is typically a free-standing membrane, or a suspended membrane, that is the sides of the membrane are connected to the (side) wall(s) of the chamber, and typically no further support/attachment/contact or the like is provided to the membrane. A reason thereto is that the
35 present membrane should be allowed to freely flex or bend under application of the pressure. The chamber, and likewise the microneedle, is typically substantially cylindrical, wherein the needle tip may be cone-shaped. It may be of any shape however, such as ellipsoidal, hexagonal, rectangular, multigonal, square, or a combination thereof. For instance, when applied

in a microscope a shape fitting an microneedle uptake element in the microscope may be preferred, such as in order to firmly confine the microneedle.

In a second aspect the present invention relates to a method for fluid manipulation comprising providing a microneedle according to the invention, providing a fluid, moving
5 the microneedle tip into the fluid, providing an under-pressure in the channel, such as an under-pressure of 1-90 kPa, typically of 10-80 kPa, aspirating the fluid in de needle tip and lower part of the microchamber, transferring the microneedle, providing an over-pressure in the channel, such as an over-pressure of 1-500 kPa, typically of 10-400 kPa, and dispensing the fluid.

10 The present invention provides a solution to one or more of the above mentioned problems and overcomes drawbacks of the prior art.

Advantages of the present description are detailed throughout the description.

DETAILED DESCRIPTION OF THE INVENTION

In an exemplary embodiment of the present microneedle the membrane has a stiff-
15 ness of < 150 N/m, preferably < 100 N/m, more preferably from 10-50 N/m, such as 20-35 N/m.

In an exemplary embodiment of the present microneedle the membrane is flexible, such as with a Youngs modulus (specific modulus) of < 2000 GPa, preferably < 2 GPa, preferably < 1 GPa, such as < 0.1 GPa, and preferably > 50 kPa, such as > 100 kPa.

20 Such a stiffness and elasticity provide sufficient strength to the membrane, and yet allow the membrane to deform under pressure, such that a liquid can be aspirated or dispensed, respectively. For instance a deformation of about 10^{-3} μm per under a pressure of about 10 Pa.

In an exemplary embodiment of the present microneedle a cross-sectional area of the
25 fluid connection between the fluid channel and the upper part of the chamber the membrane is 5-90% of a surface area of the membrane, preferably 10-50% thereof, such as 15-25% thereof. Said fluid connection is thus smaller than the membrane, and therewith inherently controls and limits the deformation of the membrane when an under pressure is applied.

In an exemplary embodiment of the present microneedle the chamber 2 may comprise
30 a membrane deformation restriction extension 8, typically an extension over a part or over a full circumference of the fluid connection of the upper part of the chamber to the channel.

In an exemplary embodiment of the present microneedle the membrane comprises a material selected from dielectric materials, such as oxides, nitrides, carbides, preferably wherein with Si, from semiconducting materials, such as Si, from polymers, from graphene,
35 and from resins.

In an exemplary embodiment of the present microneedle in use the membrane prevents liquids to pass the membrane from the needle tip to the channel.

In an exemplary embodiment of the present microneedle the membrane comprises at least one opening (5) for releasing air, such as at least one opening with an area of 10^{-4} - 10^2

μm^2 , preferably an area of 10^{-2} - $10^1 \mu\text{m}^2$, such as an area of $5 \cdot 10^{-2}$ - $5 \mu\text{m}^2$.

In an exemplary embodiment of the present microneedle the membrane comprises 1 - 10^4 openings (5)/ mm^2 for releasing air, preferably 5 - 10^3 openings (5)/ mm^2 , such as 10 - 10^2 openings (5)/ mm^2 .

5 With said openings possible entrainment of air or in general a gas underneath the membrane is prevented, as it is released through the openings to the channel.

In an exemplary embodiment of the present microneedle the at least one opening is located in a centre of the membrane, such as in a central area of the membrane comprising $<20\%$ of the surface area of the membrane.

10 In an exemplary embodiment of the present microneedle an external circumference of the needle tip is cylindrical or tapered, such as tapered under an angle α of 1 - 60 degrees relative to a longitudinal axis of the needle, preferably 2 - 45 degrees, such as 5 - 30 degrees.

In an exemplary embodiment of the present microneedle at least part of an internal circumference of the needle tip is tapered, such as tapered under an angle of 1 - 45 degrees relative to a longitudinal axis of the needle, preferably 2 - 35 degrees, such as 5 - 25 degrees.

15 In an exemplary embodiment of the present microneedle the membrane is provided centrally in said chamber, such as at a height of 40 - 60% of said chamber, e.g. a height of 45 - 55% .

In an exemplary embodiment the present microneedle may comprise a pump for providing over pressure or under pressure, respectively.

In an exemplary embodiment of the present microneedle the membrane has a thickness of 0.5 - $5 \mu\text{m}$, in particular 0.8 - $3 \mu\text{m}$, such as 1 - $2 \mu\text{m}$.

In an exemplary embodiment of the present microneedle the tip has an outer cross-sectional dimension of 500 nm - $20 \mu\text{m}$, preferably of 1 - $15 \mu\text{m}$.

25 In an exemplary embodiment of the present microneedle the tip has a height of 2 - $200 \mu\text{m}$, in particular 5 - $100 \mu\text{m}$, such as 20 - $50 \mu\text{m}$.

In an exemplary embodiment of the present microneedle the fluid channel has an outer cross-sectional dimension of 5 - $50 \mu\text{m}$.

30 In an exemplary embodiment of the present microneedle the fluid channel has a height of 2 - $20 \mu\text{m}$.

In an exemplary embodiment of the present microneedle the microneedle has an internal volume of 1 - $10^5 \mu\text{m}^3$, in particular 5 - $10^4 \mu\text{m}^3$, such as 10 - $10^3 \mu\text{m}^3$.

35 In an exemplary embodiment of the present microneedle the membrane is hydrophobic, or hydrophilic, or lipophilic, or lipophobic, or polar, or non-polar, or a combination thereof (comprising different materials).

In an exemplary embodiment the present microneedle may be obtained by semiconductor processing, such as MEMS technology.

In an exemplary embodiment of the present microneedle the microneedle is 3D-printed, such as using methods such as 2-photon polymerisation or stereolithography among

others.

In an exemplary embodiment of the present microneedle the microneedle is a monolithic needle and preferably formed from a single material.

In an exemplary embodiment of the present microneedle the microneedle is integral
5 (i.e. composed of integral parts, integrated).

In an exemplary embodiment of the present microneedle the microneedle is a single needle.

In an exemplary embodiment of the present microneedle the microneedle comprises an actuator, such as a pressure actuator, for controlling a pressure in the channel and/or chamber, such as for providing an under pressure 1-90,000 Pa or an over pressure of 100-500,000 Pa.
10

In an exemplary embodiment of the present microneedle the microneedle is calibrated. Possibly some minor production flaws may occur, and then calibration is preferred. Typically only a small fraction (e.g. ppms) may need to be calibrated and/or tested in this respect.
15

In an exemplary embodiment of the present microneedle the microneedle comprises a volume of $0.1\text{-}10^4$ femtoliter (10^{-15} L is $1\text{ }\mu\text{m}^3$), such as 0.1 femtoliter, 1 femtoliter, 2 femtoliter, 5 femtoliter, 10 femtoliter, 20 femtoliter, 50 femtoliter, 100 femtoliter, 1000 femtoliter, and 10000 femtoliter,
20 wherein the internal volume of the needle tip is from $0.1\text{-}0.5\cdot 10^4$ femtoliter, wherein the volume of the chamber accessible from the needle tip is from $0.1\text{-}0.5\cdot 10^4$ femtoliter.

In an exemplary embodiment of the present method the under-pressure and/or over-pressure are provided by a pressure actuator. For example, the needle can also be used to pick and place objects by applying under-pressure and over-pressure on the membrane respectively, and/or to study adhesion strength of cells (or objects) with a surface.
25

In an exemplary embodiment of the present method the fluid is dispensed in a biological cell. In example thereof is gene editing in single cells, such as by injecting CRISPR-Cas 9,
30

In an exemplary embodiment of the present method the fluid is aspirated from a biological cell, such as by extraction, or by biopsy. Such may be used for removing constituents from a single-cell, such as organelles.

In an exemplary embodiment of the present method the microneedle is applied in a microscope, such as in an atomic force microscope, or in an electron microscope. For example, by placing the aperture on the side (instead of apex) of the pyramidal fluid reservoir, the needle tip can be kept sharp and used in atomic force microscopy, while being used for manipulating liquids.
35

In an exemplary embodiment of the present method the fluid comprises at least one biologically or chemically active compound, such as a medicament, or a drug, or a label, or a

marker, such as a fluorescent or a phosphorescent.

In an exemplary embodiment of the present method a response of said cell is measured.

5 In an exemplary embodiment of the present method deflection of the membrane is monitored.

The invention will hereafter be further elucidated through the following examples which are exemplary and explanatory of nature and are not intended to be considered limiting of the invention. To the person skilled in the art it may be clear that many variants, being obvious or not, may be conceivable falling within the scope of protection, defined by the
10 present claims.

FIGURES

Figure 1 shows a schematic cross-section of the present device.

Figures 2a-2c show function of the present microneedle.

Figure 3 shows a cross-section of the microneedle with a hole.

15 Figures 4a-b 3 show a cross-section of the microneedle without and with a hole, respectively, as well as some dimensions thereof.

Figure 5 shows a pressure response diagram.

DETAILED DESCRIPTION OF FIGURES

In the figures:

- | | | |
|----|----|--|
| 20 | 10 | microneedles |
| | 1 | fluid channel |
| | 2 | chamber |
| | 3 | needle tip |
| | 4 | membrane |
| 25 | 5 | opening |
| | 8 | membrane deformation restriction extension |

Figure 1 shows a schematic cross-section of the present device, as detailed throughout the description..

Figures 2a-2c show function of the present microneedle. In fig. 2a a “neutral” pressure of 100 kPa is provided in the channel, in fig. 2b an under pressure is provided causing the membrane to deform and to flex, therewith causing aspiration of a liquid, of which a drop is released when the pressure applied is again 100 kPa (fig. 2c).
30

Figure 3 shows a cross-section of the microneedle with a hole.

Figures 4a-b 3 show a cross-section of the microneedle without and with a hole, respectively, as well as some dimensions thereof.
35

Figure 5 shows a pressure response diagram.

Examples of fabrication processes are 3D printing using e.g. 2-photon polymerization. Liquid photo-resist formulations that are use are for instance IP-L and IP-L 780 from Nanoscribe, in combination with a laser lithographic system. An acrylic photoresist, such as

IP-G and IP-G 780 may also be used.

CLAIMS

1. Microneedle (10) for precise fluid manipulation, in particular for aspirating and dispensing, comprising

a chamber (2) for providing a fluid,

a fluid channel (1), the fluid channel in fluid connection with an upper part of the chamber, and a

needle tip (3) in fluid connection with a lower part of the chamber,

wherein the chamber comprises a membrane (4), wherein the membrane extends fully over the fluid connection of the chamber and prevents liquid flow from a lower part of the chamber to the upper part of the chamber, and vice versa.

2. Microneedle according to claim 1, wherein the membrane has a stiffness of < 150 N/m, preferably < 100 N/m, and/or

wherein the membrane is flexible, such as with a Young's modulus of < 2000 GPa, preferably < 2 GPa, preferably < 1 GPa, such as < 0.1 GPa.

3. Microneedle according to claim 1 or 2, wherein a cross-sectional area of the fluid connection between the fluid channel and the upper part of the chamber the membrane is 5-90% of a surface area of the membrane, preferably 10-50% thereof, such as 15-25% thereof, and/or wherein the chamber (2) comprises a membrane deformation restriction extension (8), in particular an extension over a part or over a full circumference of the fluid connection of the upper part of the chamber to the channel.

4. Microneedle according to any of claims 1-3, wherein the membrane comprises a material selected from dielectric materials, such as oxides, nitrides, carbides, preferably wherein with Si, from semiconducting materials, such as Si, from polymers, from graphene, and from resins, and/or

wherein in use the membrane prevents liquids to pass the membrane from the needle tip to the channel.

5. Microneedle according to any of claims 1-4, wherein the membrane comprises at least one opening (5) for releasing air, such as at least one opening with an area of 10^{-4} - 10^2 μm^2 , preferably an area of 10^{-2} - 10^1 μm^2 , such as an area of $5 \cdot 10^{-2}$ - 5 μm^2 , and/or

wherein the membrane comprises 1 - 10^4 openings (5)/ mm^2 for releasing air, preferably 5 - 10^3 openings (5)/ mm^2 , such as 10 - 10^2 openings (5)/ mm^2 .

6. Microneedle according to claim 5, wherein the at least one opening is located in a centre of the membrane, such as in a central area of the membrane comprising $< 20\%$ of the surface area of the membrane.

7. Microneedle according to any of claims 1-6, wherein an external circumference of the needle tip is tapered, such as tapered under an angle α of 1-60 degrees relative to a longitudinal axis of the needle, and/or

wherein at least part of an internal circumference of the needle tip is tapered, such as tapered under an angle of 1-45 degrees relative to a longitudinal axis of the needle.

8. Microneedle according to any of claims 1-7, wherein the membrane is provided centrally in said chamber, such as at a height of 40-60% of said chamber.
9. Microneedle according to any of claims 1-8, comprising a pump.
10. Microneedle according to any of claims 1-9,
- 5 wherein the membrane has a thickness of 0.5-5 μm , and/or
wherein the tip has an outer cross-sectional dimension of 500 nm-20 μm , and/or
wherein the tip has a height of 2-200 μm , and/or
wherein the fluid channel has an outer cross-sectional dimension of 5-50 μm , and/or
wherein the fluid channel has a height of 2-20 μm , and/or
- 10 wherein the microneedle has an internal volume of $1-10^5 \mu\text{m}^3$.
11. Microneedle according to any of claims 1-10, wherein the membrane is hydrophobic, or hydrophilic, or lipophilic, or lipophobic, or polar, or non-polar, or a combination thereof.
12. Microneedle according to any of claims 1-11, obtained by semiconductor processing, such as MEMS technology.
- 15 13. Microneedle according to any of claims 1-12, wherein the microneedle is 3D-printed.
14. Microneedle according to any of claims 1-13, wherein the microneedle is a monolithic needle and preferably formed from a single material.
15. Microneedle according to any of claims 1-14, wherein the microneedle is integral, and/or wherein the microneedle is a single needle.
- 20 16. Microneedle according to any of claims 1-15, wherein the microneedle comprises an actuator, such as a pressure actuator, for providing a pressure in the channel and/or chamber, such as for providing an under pressure 1-90,000 Pa or an over pressure of 100-500,000 Pa.
17. Microneedle according to any of claims 1-16, wherein the microneedle is calibrated.
18. Microneedle according to any of claims 1-17, wherein the microneedle comprises a volume of $0.1-10^4$ femtoliter, such as 0.1 femtoliter, 1 femtoliter, 2 femtoliter, 5 femtoliter, 10 femtoliter, 20 femtoliter, 50 femtoliter, 100 femtoliter, 1000 femtoliter, and 10000 femtoliter,
- 25 wherein the internal volume of the needle tip is from $0.1-0.5 \cdot 10^4$ femtoliter,
wherein the volume of the chamber accessible from the needle tip is from $0.1-0.5 \cdot 10^4$ femtoliter,
- 30 19. Method for fluid manipulation comprising
providing a microneedle according to any of claims 1-18,
providing a fluid,
moving the microneedle tip into the fluid,
- 35 providing an under-pressure in the channel, such as an under-pressure of 1-90 kPa,
aspirating the fluid in the needle tip and lower part of the microchamber,
transferring the microneedle,
providing an over-pressure in the channel, such as an over-pressure of 1-500 kPa, and
dispensing the fluid.

20. Method for fluid manipulation according to claim 19, wherein the under-pressure and/or over-pressure are provided by a pressure actuator.

21. Method for fluid manipulation according to claim 19 or 20, wherein the fluid is dispensed in a biological cell, or

5 wherein the fluid is aspired from a biological cell, such as by extraction, or by biopsy.

22. Method for fluid manipulation according to any of claims 19-21, wherein the microneedle is applied in a microscope, such as in an atomic force microscope, or in an electron microscope.

10 23. Method for fluid manipulation according to any of claims 19-22, wherein the fluid comprises at least one biologically or chemically active compound, such as a medicament, or a drug, or a label, or a marker, such as a fluorescent or a phosphorescent.

24. Method for fluid manipulation according to any of claims 21-23, wherein a response of said cell is measured.

15 25. Method for fluid manipulation according to any of claims 21-24, wherein deflection of the membrane is monitored.

1/2

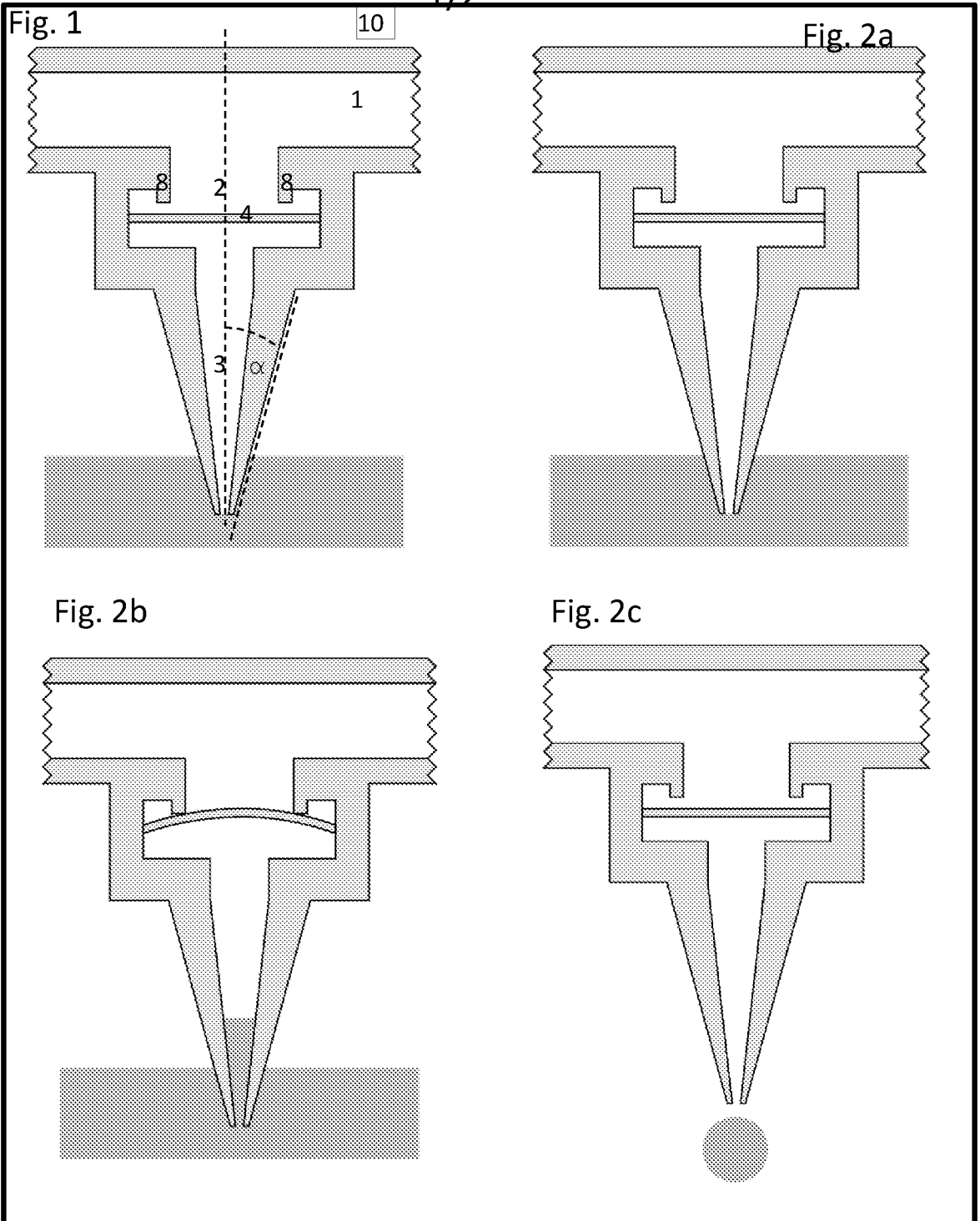
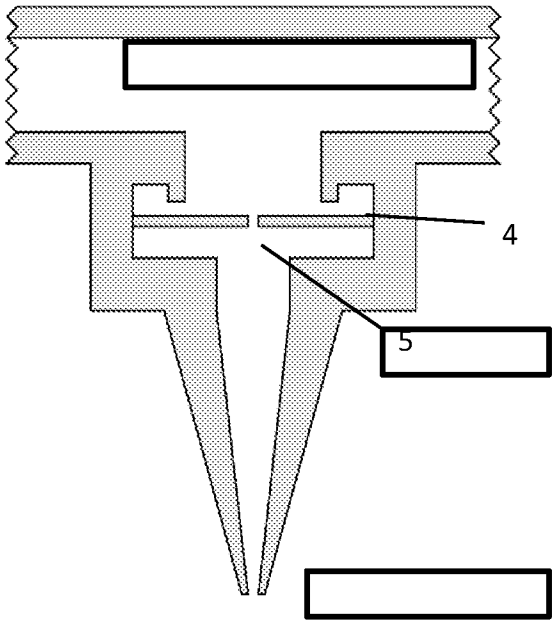


Fig. 3



2/2
Fig. 4a

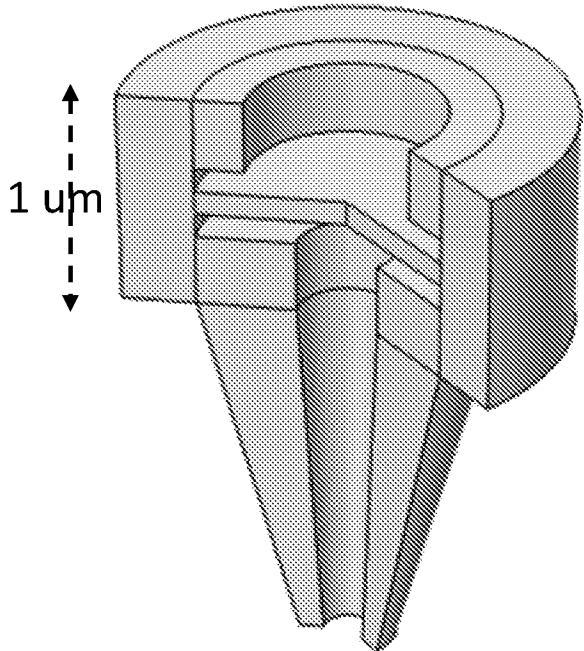


Fig. 4b

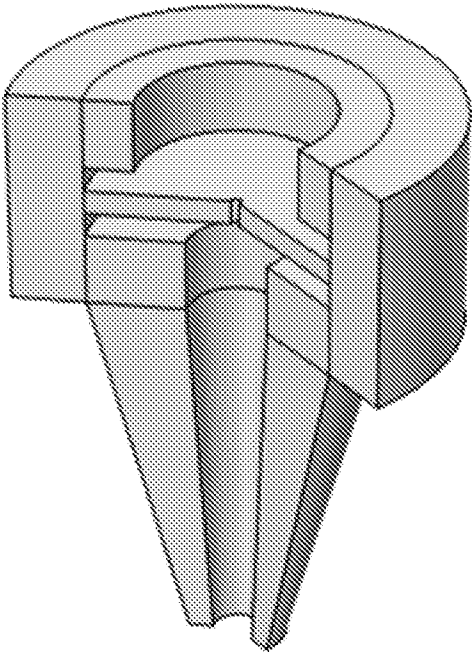
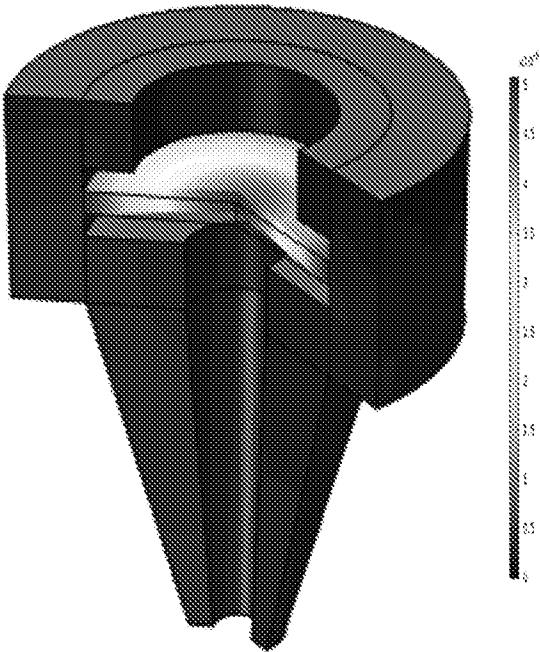


Fig. 5



INTERNATIONAL SEARCH REPORT

International application No

PCT/NL2021/050639

A. CLASSIFICATION OF SUBJECT MATTER

INV. F04B19/00 F04B43/02 F04B43/06

ADD.

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)

F04B

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 practicable, search terms used)

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	US 2011/172639 A1 (MOGA BENJAMIN J [US] ET AL) 14 July 2011 (2011-07-14) the whole document -----	1-4, 7, 9, 10, 14-18 5, 6, 8, 11-13, 19-25
X	US 2014/377091 A1 (DELEVOYE ELISABETH [FR] ET AL) 25 December 2014 (2014-12-25) the whole document -----	1, 3, 4, 7, 9-11, 14, 15, 17, 18
A	US 2010/189573 A1 (WALTERS RANDALL [US]) 29 July 2010 (2010-07-29) the whole document -----	1-25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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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

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

14 December 2021

Date of mailing of the international search report

22/12/2021

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/NL2021/050639

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011172639 A1	14-07-2011	NONE	
US 2014377091 A1	25-12-2014	EP 2758664 A1	30-07-2014
		FR 2980535 A1	29-03-2013
		US 2014377091 A1	25-12-2014
		WO 2013041700 A1	28-03-2013
US 2010189573 A1	29-07-2010	NONE	