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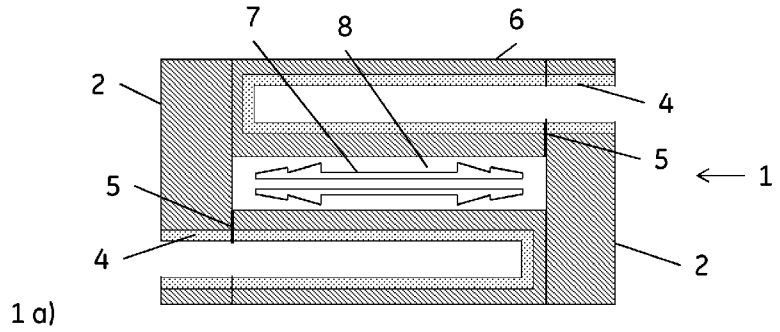

1 a)

(57) Abstract: The invention discloses an apparatus 1;11;61 for substantially sterile connection of flexible tubing, comprising: i) At least one tubing holder 2;12;62, which is adapted to receive one or more lengths of flexible tubing 3;13;63and which is also equipped with one or more sterilant applicators4;14;64. The sterilant applicator(s) is/are adapted to apply a sterilant to the or each said lengths of tubing 3;13;63when the tubing length(s) is/are received in the tubing holder 2;12;62. ii) At least one cutter 5;15;65, which is movable in relation to the tubing holder 2;12;62and adapted to cut the length(s) of tubing 3;13;63and iii) A connector holder 6;16;66, which includes a compartment 8;18;68 housing a substantially sterile tubing connector 7;17;67. The connector holder is movable in relation to the tubing holder 2;12;62to a position where the or each cut length of tubing 3;13;63and the sterile tubing connector 7;17;67are aligned and can be urged together.

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Apparatus and method for making a sterile connection of flexible tubing

Technical field of the invention

The present invention relates to connection of flexible tubing, and more particularly to an apparatus for substantially sterile connection of flexible tubing. The invention also relates to a method for substantially sterile connection of sterile tubing.

Background of the invention

Single use systems, also called disposable systems are more and more used in the bioprocess industry. For example separation or reaction systems such as chromatography systems, filter systems or bioreactor systems have today at least partly been provided as disposable systems. This eliminates the need for cleaning and cleaning validation before processing, in between processes and cycles or after processing before re -use as required for conventional re -usable equipment. With disposable systems cross-contamination is avoided. Bioburden control of single-use equipment during manufacturing of the equipment itself is required to eliminate cleaning needs before bringing single-use equipment into product contact. This is usually achieved by manufacturing of single-use equipment in controlled environment (clean room), often followed by sterilisation processes (gamma irradiation). The demands of the level of bioburden control can differ for different applications, however, bioburden control to a certain degree of the equipment is not only required for some applications, but also considered as the preferable for most of the applications using disposable equipment. The production of this equipment in controlled environments is required to guarantee a low initial level of contaminants prior to the bioburden control procedure, hereby reducing for example endotoxin levels.

Typical applications of aseptic connectors in biomanufacturing are connections between fluid lines, separation units (filters, chromatography columns, adsorbers, membrane adsorbers, expanded or fluidized bed adsorbers) or reaction units (bioreactors, reaction or (bio-)conversion units that for example utilize enzymatic conversions).

Sterility and asepsis are terms used to define the state of a system, a piece of equipment or a fluid conduit as being in control of bioburden levels to different degrees. Aseptic connectors can be used to interconnect single-use equipment and also single-use equipment and conventional re-use equipment that is bioburden controlled (sanitized, sterilized etc.). Available aseptic connectors are for example ReadyMate™ connectors from GE Healthcare and Kleenpack™ from Pall. These use removable protective films to ensure asepsis and are applied to lengths of tubing and/or equipment in a manufacturing operation, after which the tubing/equipment with the connectors is gamma sterilized. This means that they are only useful for preassembled circuits.

For assembly of tailor-made aseptic circuits directly at the place of use, the current approach is to use heat welding of flexible tubing. Welders for this purpose use electrically heated wafers to cut and weld tubing, and are commercially available from e.g. GE Healthcare (Sterile Tube Fuser) and Sartorius Stedim Biotech (BioWelder™). These equipments are stationary, heavy and require electrical connection.

Accordingly there is a need for lighter and more convenient devices to be used in aseptic connection of flexible tubing in e.g. bioprocessing settings.

Summary of the invention

One aspect of the invention is to provide an apparatus for substantially sterile connection of flexible tubing, which apparatus is small, has a low weight, does not require electrical connection and is generally convenient to use. This is achieved with an apparatus as defined in claim 1.

One advantage is that the apparatus can be handheld and used to connect tubing in situ, even in inconvenient locations which are not possible to access with heavy electrical welding equipment. A further advantage is that also non-weldable tubing may be connected, e.g. rubber tubing.

Another aspect of the invention is to provide a simple and convenient method for substantially sterile connection of flexible tubing directly in a bioprocess setting. This is achieved with a method as defined in the claims.

Further suitable embodiments of the invention are described in the dependent claims.

Brief description of drawings

Figure 1 shows an apparatus of the invention through the different steps of the method of the invention. 1 a) The apparatus before use. 1 b) The apparatus with two lengths of tubing inserted. 1 c) The apparatus after cutting the lengths of tubing and alignment of the tubing lengths with the connector. 1 d) The apparatus after the cut lengths of tubing and the connector have been urged together. 1 e) The removed tubing/connector assembly.

Figure 2 shows an embodiment of the apparatus of the invention with a sterilant reservoir.

Figure 3 shows an alternative embodiment of the apparatus of the invention and its use. 3 a) The apparatus with two lengths of tubing inserted. 3 b) The apparatus after the cut lengths of tubing and the connector have been urged together.

Figure 4 shows further embodiments of the apparatus, with different types of connectors. 4 a) One-way angled hose-barb connector. 4 b) T-connector.

Figure 5 shows an embodiment comprising a connector with a removable protective film/cap.

Figure 6 shows an embodiment where the connector comprises a notched metal tube.

Figure 7 shows a rotary embodiment of the apparatus of the invention. 7 a) The apparatus with two lengths of tubing inserted. 7 b) The apparatus after cutting the lengths of tubing and aligning the tubing lengths with the connector.

Detailed description of embodiments

In one aspect the present invention discloses an apparatus **1**;**11;61** for substantially sterile connection of flexible tubing, as illustrated by Figs. 1-4 and 7. This apparatus comprises:

i) At least one tubing holder **2**;**12;62**, which is adapted to receive one or more lengths of flexible tubing **3**;**13;63** and which is also equipped with one or more sterilant applicators **4**;**14;64**. The

sterilant applicator(s) is/are adapted to apply a sterilant to the or each said lengths of tubing **3;13;63** when the tubing length(s) is/are received in the tubing holder **2;12;62**. The tubing holder(s) may each comprise an essentially cylindrical port of a diameter suitable to receive a length of tubing and the port may e.g. lead into a tubing end receiver located in a connector holder **6** or into a cutting and connecting compartment **19**. The port(s) can suitably be covered with protective film(s) or cap(s), to be removed before receiving the length(s) of tubing. The sterilant applicator(s) may e.g. each be a tubular or slit tubular layer of a flexible open-porous material (e.g. a polymer foam) arranged on the inner surface of the cylindrical port(s). The sterilant applicator(s) may contain an imbibed liquid sterilant, such as hydrogen peroxide or an aqueous hydrogen peroxide solution, e.g. comprising 3 - 60 wt. % or 25-35 wt % hydrogen peroxide. The sterilant applicator(s) may also, or alternatively, be fluidically connected or fluidically connectable to a sterilant reservoir **33** comprising a liquid sterilant, such as hydrogen peroxide or an aqueous hydrogen peroxide solution, e.g. comprising 3 – 60 wt. % or 25-35 wt % hydrogen peroxide. In both cases, the sterilant can alternatively also be a solution comprising ethanol (typically a 60 – 80 wt% aqueous ethanol solution), hypochlorite (typically a 0.5 – 10 wt % aqueous sodium hypochlorite solution) etc. The use of hydrogen peroxide solutions has the advantage that any residues of hydrogen peroxide will react to form non-toxic water and oxygen. Aqueous hydrogen peroxide solutions possess germicidal properties over a concentration interval from below 1 wt % to 95-100 wt%, but the effect is more reliable and rapid at concentrations of 10 wt % and higher. Hydrogen peroxide at high concentrations may pose an explosion hazard, so 10 – 60 wt % or in particular 25 – 35 wt % is preferred.

ii) At least one cutter **5;15;65**, which is movable in relation to the tubing holder **2;12;62** and adapted to cut the length(s) of tubing **3;13;63**. The cutter(s) can be a blade or a similar device with a sharp edge, e.g. a sharp edge on a tubing holder, or it can alternatively be a heated wafer or even e.g. a laser. The cutter(s) can be movable in a direction essentially transverse to the length(s) of tubing received in the tubing holder(s). The cutter or each cutter may be movable in a plane interfacing a tubing holder and a connector holder, or a cutting and connecting compartment, in a direction towards the length of tubing received in the tubing holder. The cutter(s) can be movable independently or together with the connector holder.

iii) A connector holder **6;16;66**, which includes a compartment **8;18;68** housing a substantially sterile tubing connector **7;17;67**. The connector holder is movable in relation to the tubing holder **2;12;62** to a position where the or each cut length of tubing **3;13;63** and the sterile tubing

connector 7;**17;67** are aligned and can be urged together. The compartment suitably extends in a direction essentially parallel to the tubing port(s) and to the length(s) of tubing received in the tubing holder(s).

In some embodiments, the apparatus also comprises a sterilant reservoir **33**, adapted to supply sterilant to the sterilant applicator(s) **4**;**14;64**, such as each sterilant applicator. The sterilant reservoir may e.g. comprise a breakable ampoule **31** containing a sterilant. Such a breakable ampoule may e.g. be contained in an ampoule compartment **30**, which is fluidically connected to the or each sterilant applicator(s) via fine tubing or conduits **32** inside one or more of the tubing holder(s) and/or the connector holder. When the ampoule is broken, the sterilant will partially fill the ampoule compartment and flow towards the sterilant applicator(s) by e.g. gravity or capillary suction, filling or partially filling the sterilant applicator(s) with sterilant. The sterilant reservoir **33** may also be integrated with the or each sterilant applicator(s) **4**;**14;64**. It is e.g. possible to use one or more sterilant applicators pre-filled with sterilant and covered with e.g. a protective film which may be removed before insertion of the tubing length(s). Such a protective film or cap may e.g. be integrated with a protective film or cap covering a port, as described above. The sterilant comprised in the breakable ampoule or in the pre-filled sterilant applicator(s) may as described above be e.g. an aqueous solution comprising hydrogen peroxide, e.g. a solution comprising 3 – 60 wt % or 25 – 35 wt % hydrogen peroxide.

In certain embodiments, the apparatus further comprises a movable cover **20** (not shown in Figure 1), which in a closed position delimits a cutting and connecting compartment **9**;**19** and in an open position allows removal of the cut and connected length(s) of tubing. The device can e.g. be supplied with the cover in a closed position and presterilized by e.g. gamma irradiation, such that the cutting and connecting compartment is substantially sterile. After cutting the tubing length(s) and urging together with the connector, the cover may then be opened to allow the removal. The cover may be temporarily locked in the closed position by a removable seal or tape etc. to prevent premature opening of the cover. The movable cover **20** may be one integral cover or it may be divided into a plurality of part covers.

The apparatus **1**;**11;61** may be adapted for either linear or rotary movement of the connector holder **6**;**16;66** and cutter(s) **5**;**15;65** in relation to the tubing holder(s) **2**;**12;62**. Linear versions are illustrated in Figs. 1-4 and a rotary version in Fig. 7. Specific advantages of the rotary

version are that the cutters **65** may be easier to keep sterile and that a compact design can be achieved.

In some embodiments, the tubing connector 7;**17;67** is a hose barb connector. The tubing connector can further be e.g. a straight two-way connector 7;**17;67**, a three-way T-connector **40** or an angled connector, such as an angled two-way connector **41,** as illustrated in Fig. 4.

In certain embodiments, illustrated by Fig. 5, the tubing connector **50** comprises a port **51** covered with a removable protective film or cap **52**. Suitable such ports are described in e.g. US6679529, WO1994008173A1, which are hereby incorporated by reference in their entirety. The removable film or cap ensures that the connector with the attached tubing length(s) is substantially sterile and it can later be connected aseptically to another port with removable film or cap without having to use a LAF bench or similar.

In some embodiments, the tubing holder is adapted to receive a length of tubing at a point distant from the ends of said length of tubing. In this case the tubing holder may comprise a recess arranged to receive a portion of said length of tubing and a movable cover (either separate or forming a part of movable cover **20**) arranged to be movable from an open position to a closed position where it covers the recess with the tubing portion. One or more sterilant applicators is/are arranged to apply sterilant to the tubing portion, such as over the entire tubing portion received in the tubing holder. The sterilant applicator(s) can e.g. be wrapped around the tubing portion or may comprise one layer on the recess and one on the inside of the movable cover, such that when the movable cover is in a closed position, the tubing portion is essentially completely surrounded by the sterilant applicators. One advantage of receiving a length of tubing without receiving the ends of the length is that the apparatus can be used to disconnect a length of tubing already attached in both ends. For this purpose, the apparatus can suitably comprise two sterile tubing connectors, of which one or both can be blind connectors and/or one or both can be tubing connectors comprising a port covered with a removable protective film or cap as described above and in Fig. 5. It is of course also possible to use a three-way tubing connector as illustrated in Fig. 4 b) in order to connect a further length of tubing. If the length of tubing is filled with liquid, it is advantageous if it is drained before disconnection.

In some embodiments, illustrated by Fig. 6, the tubing connector **57** is prepared from a deformable plastic and a central part of said tubing connector is concentrically contained in a

notched metal tube **58** adapted to upon external compression cut off the tubing connector and fluidically seal off the cut tubing connector ends. At the place of the notch, the inside of the metal tube may have a sharp transverse edge, which upon compression with e.g. a pair of pliers can cut the plastic of the connector. Upon a slight bending of the compressed assembly, the connector can be cut off, leaving the ends sealed by the compressed metal tube ends. This allows for convenient aseptic disconnection once the tubing connection is no longer needed. The metal tube can suitably be made from an easily deformable metal such as e.g. aluminium. The deformable plastic may e.g. be a polyolefin such as polypropylene or polyethylene.

In certain embodiments, the or each cutter **5**;**15;65** comprises a blade or a sharp edge of the connector holder **2**;**12;62**.

In some embodiments, the apparatus has been sterilized, optionally using ionizing radiation.

In one aspect the present invention discloses a method for substantially sterile connection of flexible tubing, comprising the steps of:

a) providing the apparatus of the embodiments described above and at least one length **3**;**13;63** of flexible tubing;

b) placing the or each length of tubing in the or each tubing holder **2**;**12;62** and applying sterilant to the tubing with the or each sterilant applicator **4**;**14;64**;

c) moving the cutter or cutters **5**;**15;65** to cut the or each length of tubing;

d) moving the connector holder **6**;**16;66** to the position where the connector 7;**17;67** is aligned with the or each cut length of tubing;

e) urging the connector and the or each cut length of tubing together to form a connected assembly; and

f) removing the connected assembly from the apparatus.

The movements in c) and d) may be linear or rotational and the position in d) may be a linear position or an angular position. The flexible tubing can be flexible plastic tubing (e.g. plasticised PVC) or flexible elastomeric tubing (e.g. thermoelastomer tubing or rubber tubing, including silicone rubber). The tubing can suitably be flexible enough to allow manual cutting with a blade and is suitably free from metal reinforcements. The wall thickness of the tubing may e.g. be 0.5-5 mm, such as 1-3 mm, and the inner diameter of the tubing may e.g. be 1-20 mm, such as 2-10 mm.

The length(s) of tubing **3**;**13;63** may be sealed at both ends and presterilized, e.g. by exposure to gamma irradiation. The sealed ends may have circular cross sections to allow for easy introduction in circular cylindrical ports.

In certain embodiments the method further comprises before step b) a step of fluidically connecting the sterilant in the sterilant reservoir **33** with the or each sterilant applicator **4**;**14;64**. If the sterilant reservoir comprises a breakable ampoule **31** with sterilant (e.g. an aqueous hydrogen peroxide solution), this step may comprise the breakage of the breakable ampoule.

In some embodiments the method further comprises a step of breaking an ampoule **31** containing the sterilant.

In certain embodiments, the method further comprises a step of opening a cover **20** between steps e) and f).

This written description uses examples to disclose the invention, including the best mode, and also to enable any person skilled in the art to practice the invention, including making and using any devices or systems and performing any incorporated methods. The patentable scope of the invention is defined by the claims, and may include other examples that occur to those skilled in the art. Such other examples are intended to be within the scope of the claims if they have structural elements that do not differ from the literal language of the claims, or if they include equivalent structural elements with insubstantial differences from the literal languages of the claims.

CLAIMS

1. An apparatus (1;11;61) for substantially sterile connection of flexible tubing, comprising:
at least one tubing holder (2;12;62), adapted to receive one or more lengths of said tubing (3;13;63) and equipped with one or more sterilant applicators (4;14;64) adapted to apply a sterilant to the or each said length of tubing (3;13;63) upon reception of the tubing length(s) in the tubing holder (2;12;62);
at least one cutter (5;15;65), movable in relation to the tubing holder (2;12;62) and adapted to cut the or each said length of tubing (3;13;63); and
a connector holder (6;16;66) including a compartment (8;18;68) housing a substantially sterile tubing connector (7;17;67), said connector holder being movable in relation to the tubing holder (2;12;62) to a position where the or each cut length of tubing (3;13;63) and the sterile tubing connector (7;17;67) are aligned and can be urged together.

2. The apparatus of claim 1, further comprising a sterilant reservoir (33), adapted to supply sterilant to the or each sterilant applicator (4;14;64).

3. The apparatus of claim 2, wherein the sterilant reservoir (33) comprises a breakable ampoule (31) containing a sterilant.

4. The apparatus of claim 4, wherein the sterilant comprised in the breakable ampoule is an aqueous solution comprising hydrogen peroxide, such as a solution comprising 3 – 60 wt % or 25 – 35 wt % hydrogen peroxide.

5. The apparatus according to any preceding claim, further comprising a movable cover (20), which in a closed position delimits a cutting and connecting compartment (9;19) and in an open position allows removal of the cut and connected length(s) of tubing.

6. The apparatus according to any preceding claim, wherein the tubing connector (7;17;67) is a hose barb connector.

7. The apparatus according to any preceding claim, wherein the tubing connector (50) comprises a port (51) covered with a removable protective film or cap (52).

8. The apparatus of any preceding claim, wherein a tubing holder is adapted to receive a length of tubing at a point distant from the ends of said length of tubing.

9. The apparatus according to any preceding claim, wherein the tubing connector (57) is prepared from a deformable plastic and a central part of said tubing connector is concentrically contained in a notched metal tube (58) adapted to upon external compression cut off the tubing connector and fluidically seal off the cut tubing connector ends.

10. The apparatus according to any preceding claim, wherein the or each cutter (5;15;65) comprises a blade or a sharp edge of the connector holder (2;12;62).

11. The apparatus according to any preceding claim, which has been sterilized, optionally using ionizing radiation.

12. The apparatus according to any preceding claim, wherein said cutter(s) and connector holder are rotationally or linearly movable in relation to said tubing holder(s).

13. A method for substantially sterile connection of flexible tubing, comprising the steps of:
a) providing the apparatus (1;11;61) of any preceding claim and at least one length of flexible tubing (3;13;63);
b) placing the or each length of tubing in the or each tubing holder (2;12;62) and applying sterilant to the tubing with the or each sterilant applicator (4;14;64);
c) moving the cutter (5;15;65) or cutters to cut the or each length of tubing;
d) moving the connector holder to the position where the connector (7;17;67) is aligned with the or each cut length of tubing;
e) urging the connector and the or each cut length of tubing together to form a connected assembly; and
f) removing the connected assembly from the apparatus.

14. The method of claim 13, further comprising before step b) a step of fluidically connecting the sterilant in the sterilant reservoir (33) with the or each sterilant applicator.

15. The method of claim 14, further comprising a step of breaking an ampoule (31) containing the sterilant.

16. The method of any one of claims 13-15, wherein the cutter(s) and connector holder are rotationally or linearly moved.

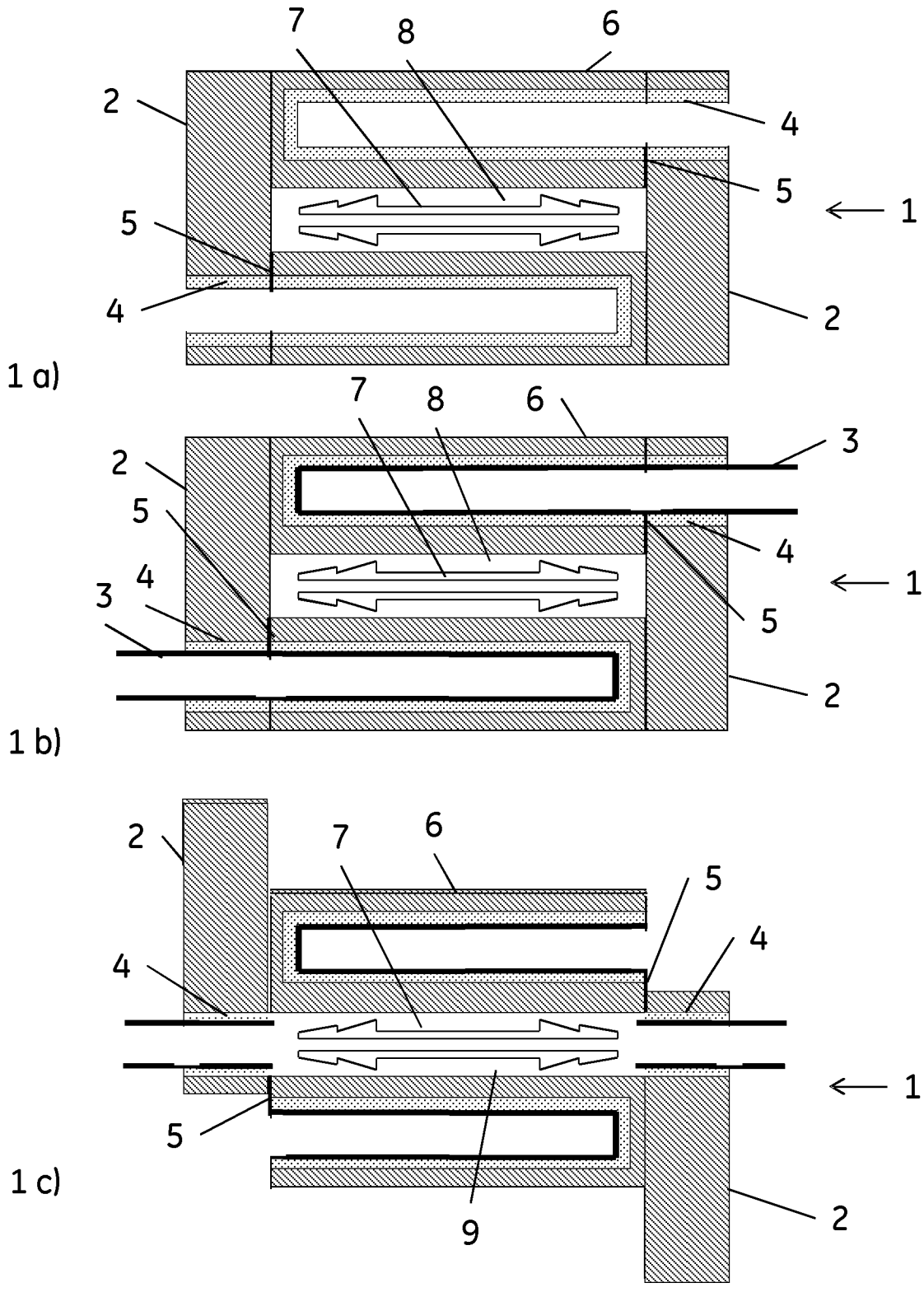
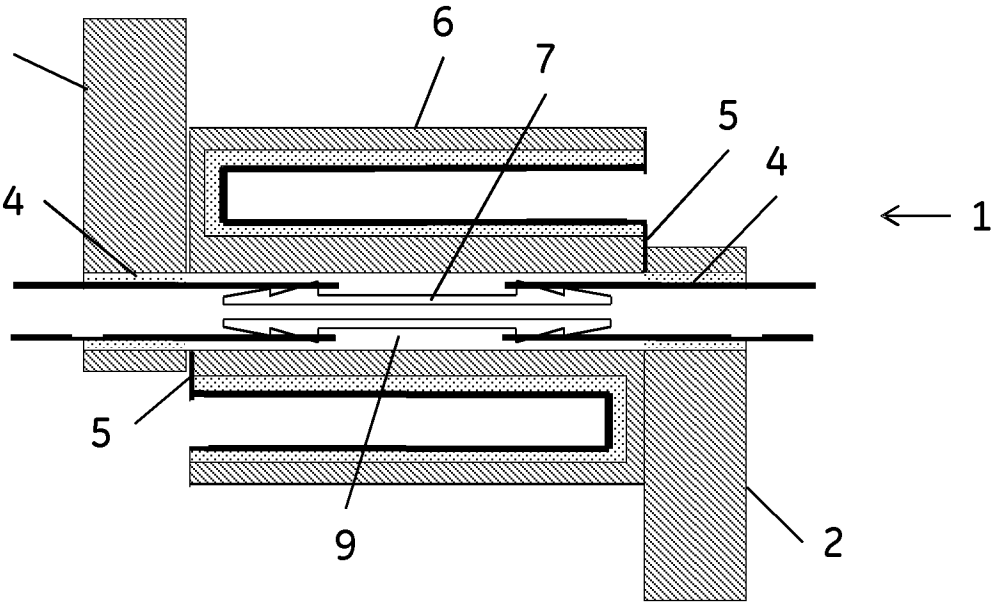
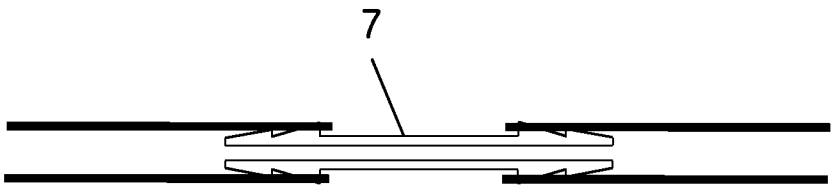


Fig. 1.



1 d)



1 e)

Fig. 1.

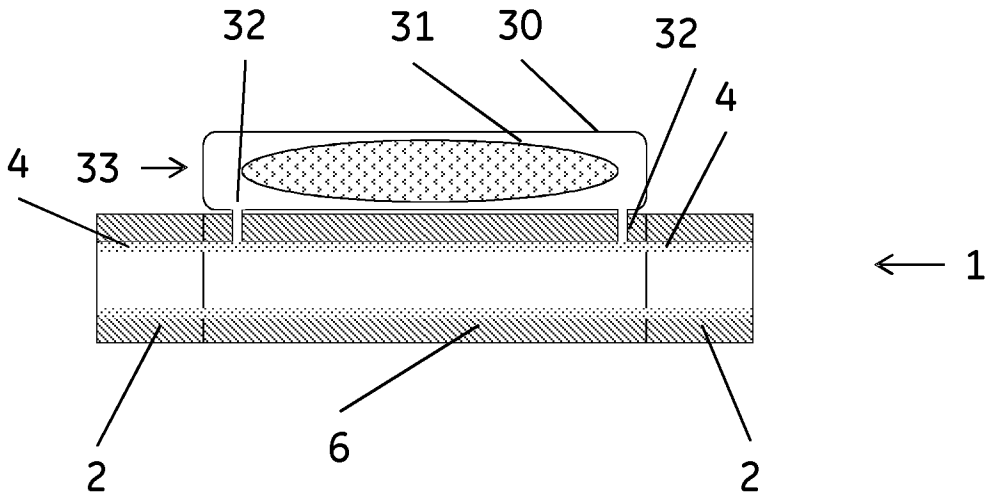
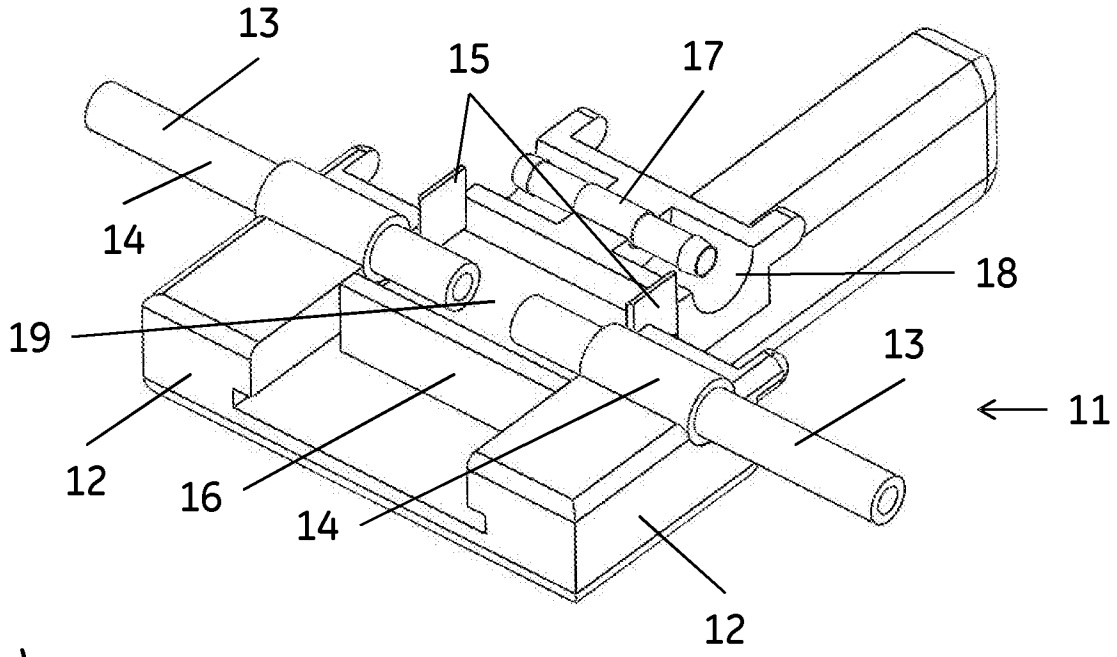
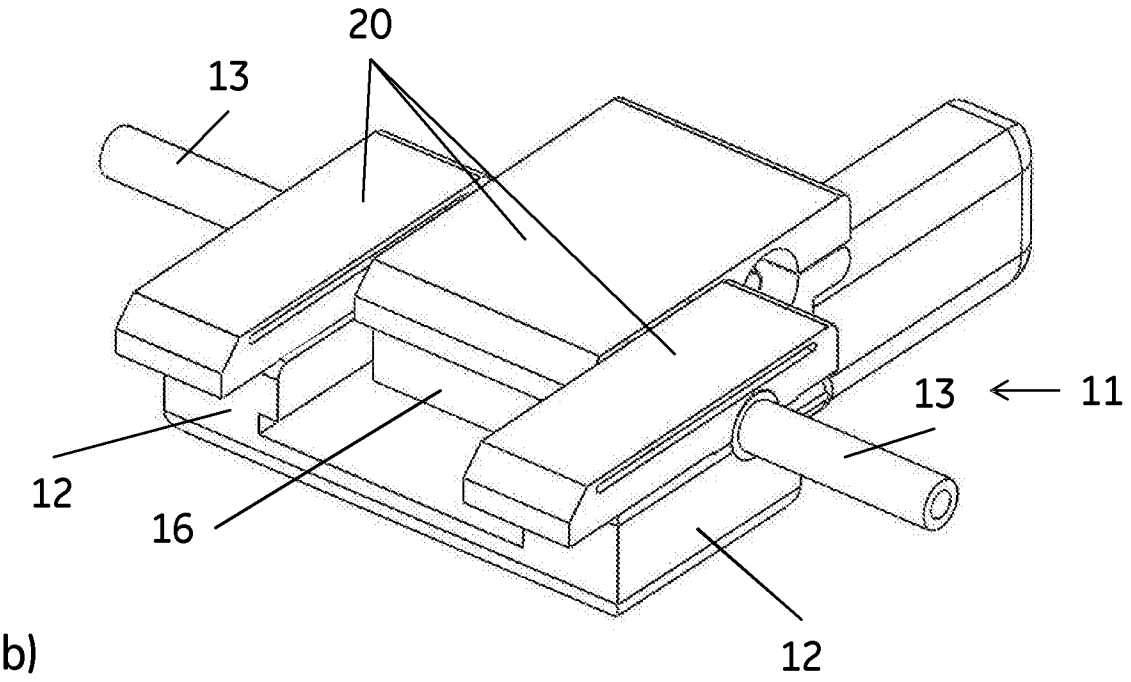


Fig. 2.

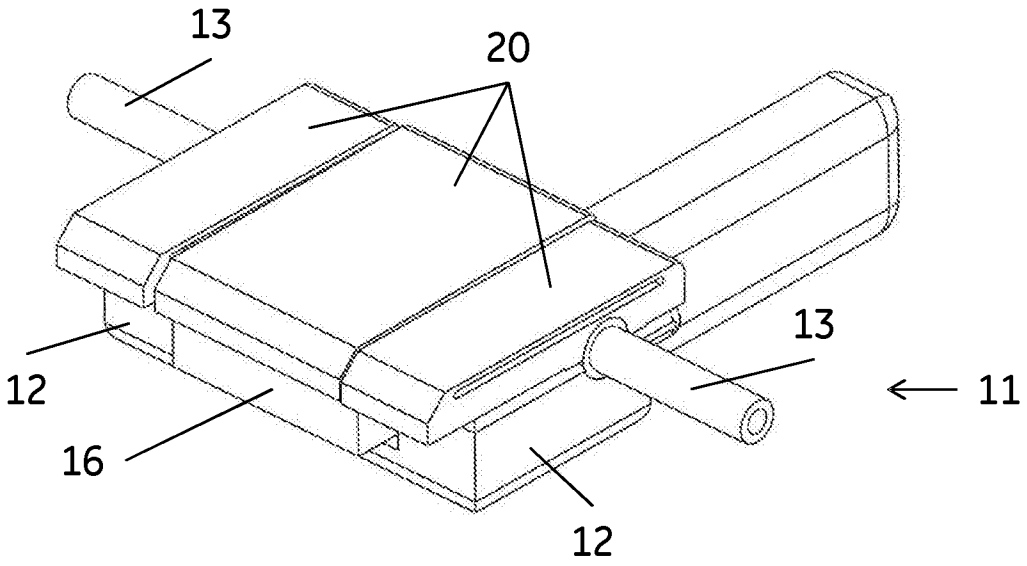


a)

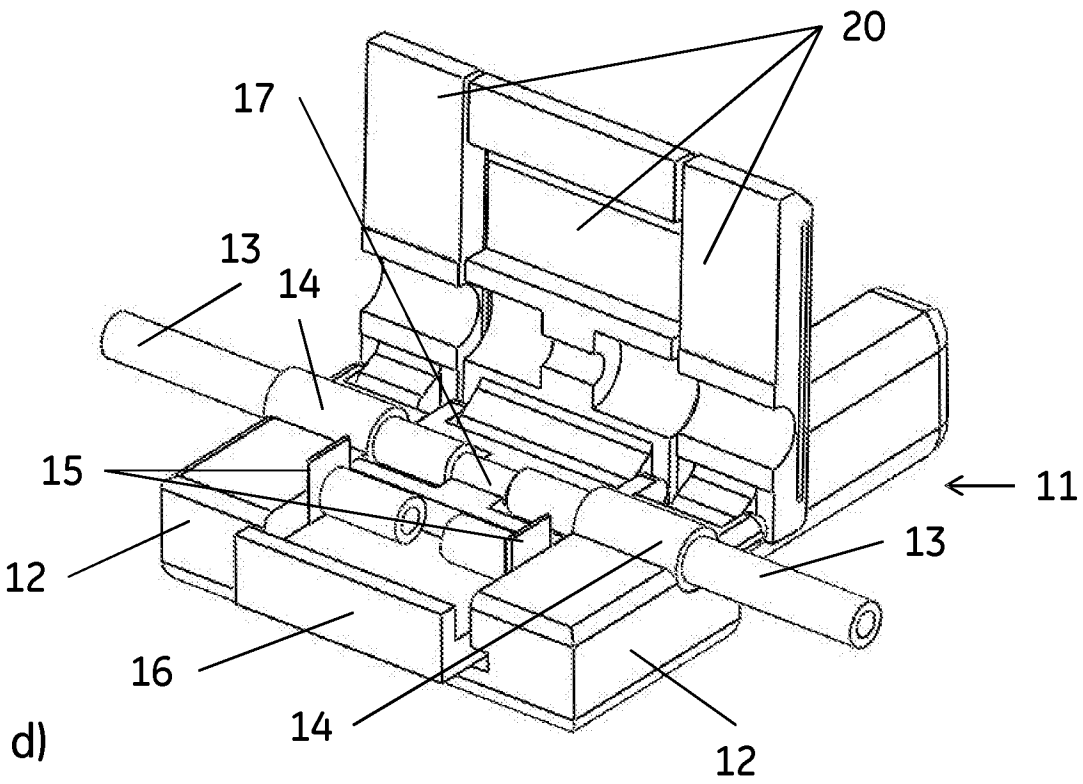


b)

Fig. 3.

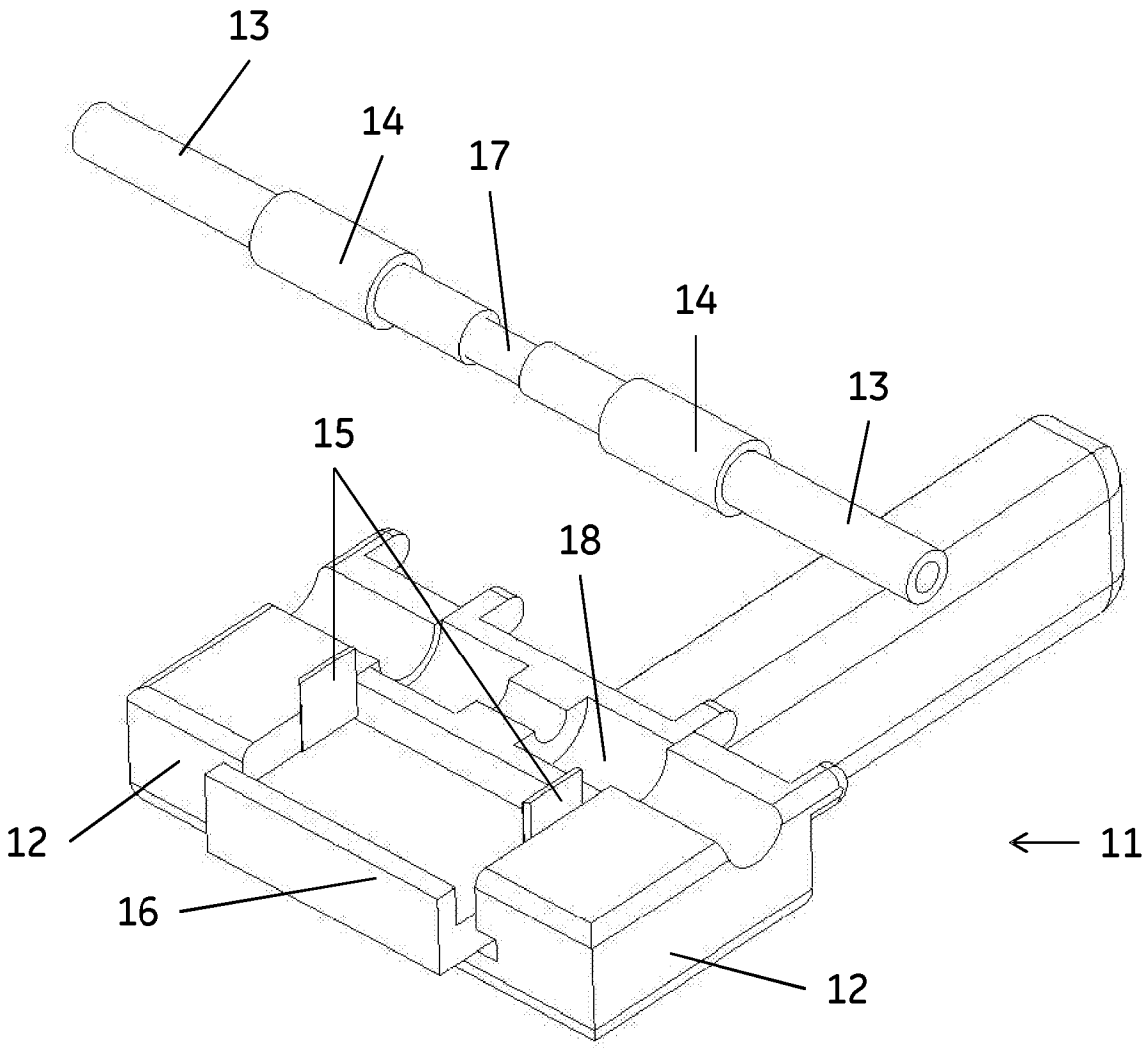


c)



d)

Fig. 3.



e)

Fig. 3.

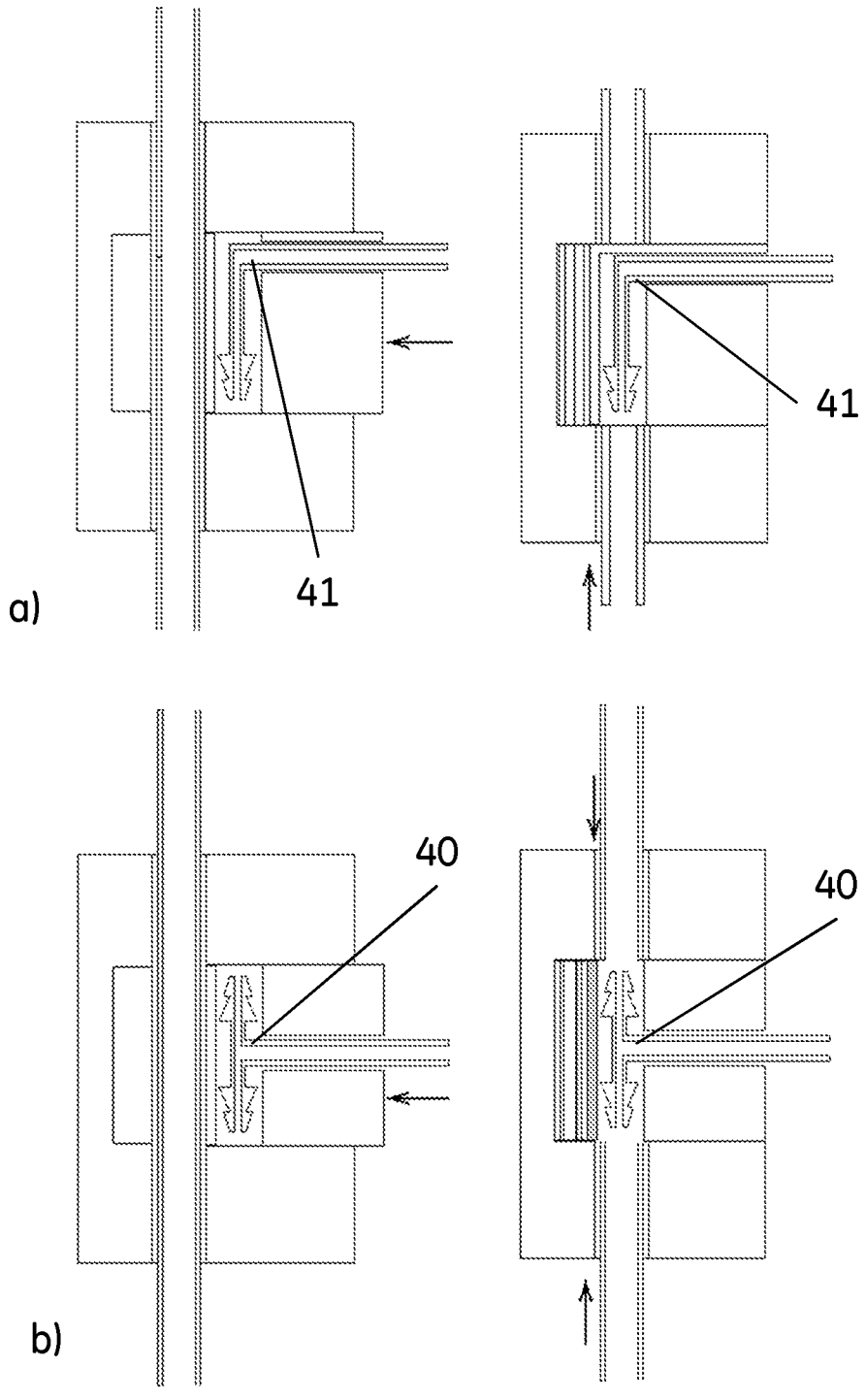
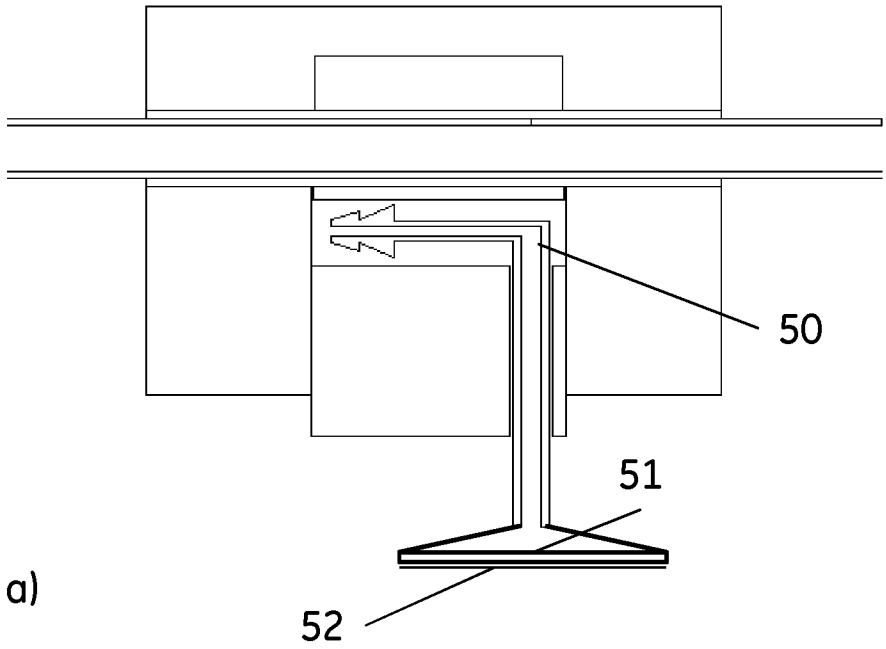
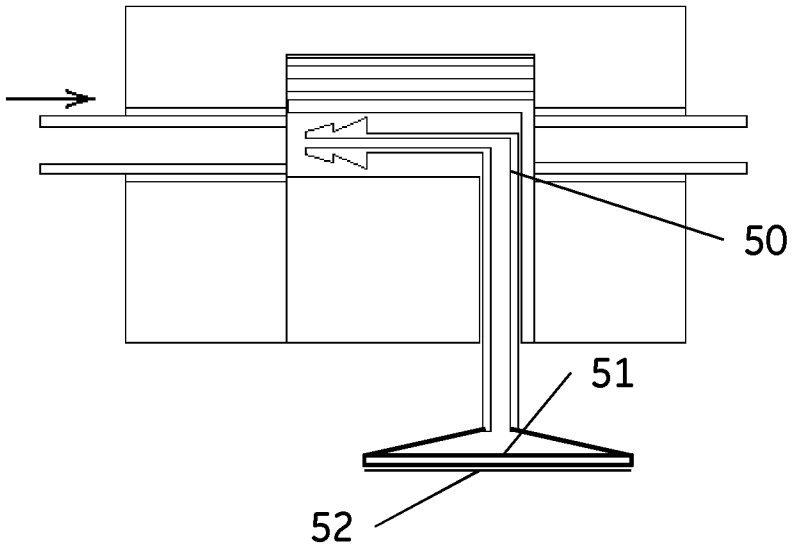


Fig. 4.



a)



b)

Fig. 5.

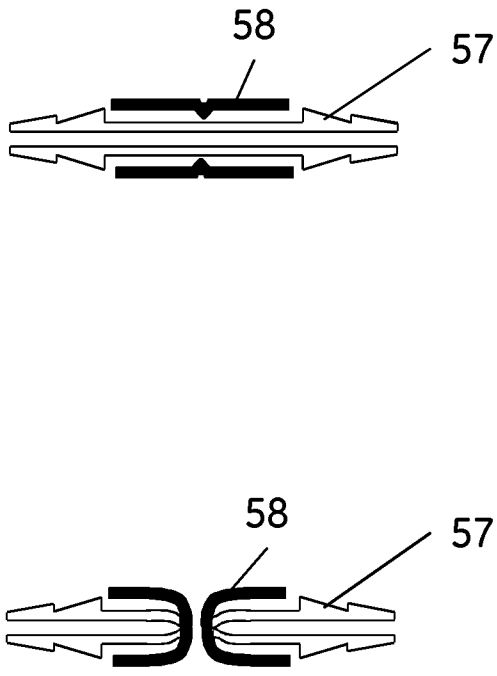


Fig. 6.

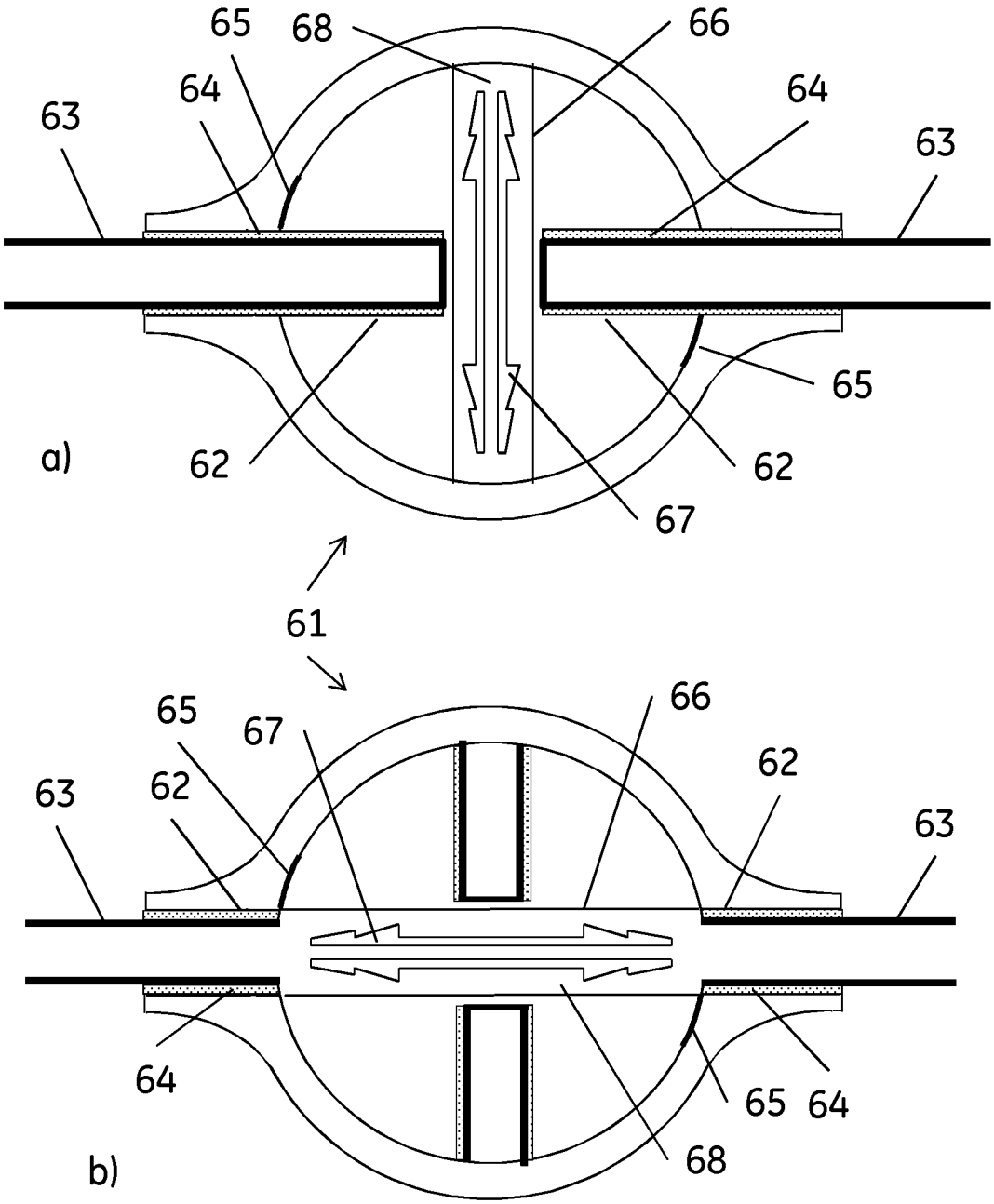


Fig. 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2014/050609

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61M, F16L

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

SE, DK, FI, NO classes as above

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

EPO-Internal, PAJ, WPI data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0507321 A1 (TERUMO CORP), 7 October 1992 (1992-10-07); whole document --	1-16
A	US 6524304 B1 (PICOU GREG ET AL), 25 February 2003 (2003-02-25); whole document --	1-16
A	US 5965086 A (ROSE SAM ET AL), 12 October 1999 (1999-10-12); whole document -- --------	1-16

☐ 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
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"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
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09-10-2014	09-10-2014

Name and mailing address of the ISA/SE	Authorized officer
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International application No.
PCT/SE2014/050609

Continuation of: second sheet

International Patent Classification (IPC)

A61M 39/18 (2006.01)
F16L 21/00 (2006.01)
F16L 37/02 (2006.01)

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