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(54) Title: MICROFLUIDIC DEVICE AND METHOD FOR BATCH ADSORPTION

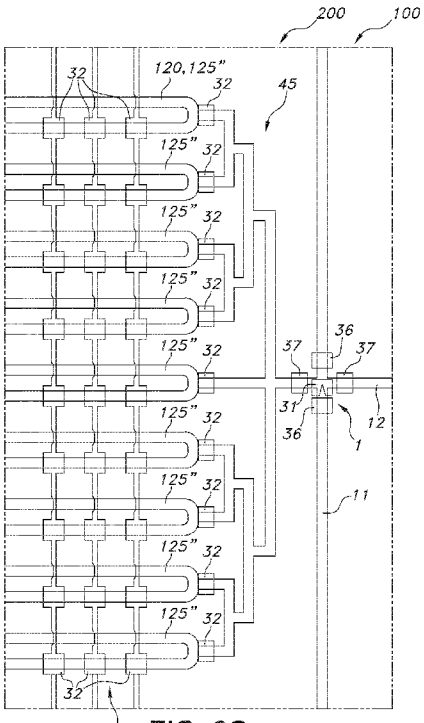

FIG. 6C

(57) Abstract: The invention relates to a fluidic device (1) having a particle trap functionality for a particle (2) in a fluid, the fluidic device (1) comprising a first fluid flow channel (11), a second fluid flow channel (12), and a control channel (13), wherein the first fluid flow channel (11) is in fluid contact with the second fluid flow channel (12) and intersects the second fluid flow channel (12) at an intersection (14), wherein the control channel (13) at the location of the intersection (14) is arranged adjacent to the first fluid flow channel (11) and separated by a flexible membrane (17) from the intersection (14), wherein the flexible membrane (17) is configured as a valve (31), configured in operation at a first pressure in the control channel (13) in a first position not to block propagation of a particle (2) of a predetermined size in the first fluid flow channel (11), and at a second pressure in the control channel (13) in a second position to block with said flexible membrane (17) propagation of said particle (2) through the first fluid flow channel (11), while in this second position not fully blocking fluid flow through the first fluid flow channel (11) wherein the valve (31) is configured to provide in said second position a gradual increasing blockade of a cross sectional area (19) of the first fluid flow channel (11) in a direction parallel to a longitudinal axis of the first fluid flow channel (11).

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Microfluidic device and method for batch adsorption

FIELD OF THE INVENTION

The invention relates to a fluidic device and to a processing device comprising such fluidic device. The invention further relates to a method for performing a batch adsorption experiment.

BACKGROUND OF THE INVENTION

Batch adsorption/desorption equilibrium methods are useful for generating essential information on the distribution of chemicals over a solid and a fluid phase. They are also frequently used in separation and purification of industrial (bio) chemicals, or as a diagnostic tool for detecting an analyte or biomarker in a medical-clinical, environmental or other sample of which the composition needs to be determined. Furthermore, adsorption isotherms are also used for the design of dynamic/non-equilibrium separation steps e.g. chromatographic unit operations The state of the art in these fields, and particularly in the field of batch adsorption for protein purification purposes, is that determination of a batch adsorption isotherm requires vast numbers of experiments, with the drawback that large amounts of expensive or rare materials such as protein and resin, and commodities like salts and solvents are consumed. Especially, in the early stages of process development in Biopharma industry, hardly any protein product is available. Therefore, using minute amounts of protein product, to test different resins for large scale process development is very advantageous. From the start directly a proper process can be designed that can also easily be scaled-up.

SUMMARY OF THE INVENTION

During the last decade, the potential of (micro) fluidic systems to high-resolution separation is amongst others studied for proteomic and pharmaceutical applications. Also micro fluidic liquid chromatography systems that contain micro channels with patterned microstructures have shown to give higher resolution than classical or

conventional chromatography. Combination of the techniques could bring a new powerful analysis tool for separation of biomolecules.

A disadvantage that may be associated with miniaturizing is that small uncertainties in operating parameters or deviations from the presumed operating parameters may have a severe effect on the results generated by the miniaturized process. For adsorption/desorption methods, for instance, a controlled amount of particles, such as resin particles, is required. Particularly, if only a few resin particles (beads) are used in the adsorption process, small deviations from the number (and size and consequently the surface area) of the particles may result in an overestimation or underestimation of the adsorption coefficients. Consequently, many (extra) scaling-up steps may be required to design and set-up an industrial process based on the results of the initial experiments. Hence, it is desired to know the exact amount of particles used in the experiments, especially the number (and size) of particles supplied into the set-up.

A reliable way to control the amount of particles (e.g. to create a column of adsorption material or to provide a specific number of particles in a flow) in a (experimental) set-up is by supplying the particles one by one (while counting the number of particles supplied). It was found that especially (one by one) catching a particle from a particle flow containing (a diluted flow of) particles and introducing the caught particle into the set-up is a very advantageous way to provide the particles, especially in small scale systems operated with small particles (at a (sub) micrometer scale to millimeter scale). Moreover, by controlling the size of the particles also the total particle surface area loaded in the system may be controlled.

Micro fluidic particle catch systems are known in the art. For instance US20130302807 describes systems to catch a particle from a flow. However, releasing the particle (in its intact form) from the capturing unit does not seem to be possible. US20120061305, further, describes a sieve valve for use in microfluidic device. The sieve valve, however, does not seem to be applicable in controlling the amount (and size) of particles the chromatography module comprises at the end or in providing a specific number of particles in a flow.

US2014034556 describes a particle separation microstructure comprising a body and a flow channel extending through the body, having an inlet and an outlet for receiving a flow of particles therethrough. The flow channel comprises opposing first

and second walls disposed in a spaced-apart relationship and at least one protrusion extending from the first wall into the flow channel and extending along a length of the flow channel. At least a portion of one of the first and second walls is reversibly actuatable between a first and a second position and the first and second walls are substantially parallel in the second position. In the first position the flow channel is open for receiving the flow of particles and in the second position the at least one protrusion abuts the second wall and the flow channel is constricted for restricting the flow of particles and separating particles from the flow of particles. The valve as described further may trap particles at different recesses inside a deflecting membrane valve area. The sample channel design of the device seems to require three different height levels for proper filtration operation, requiring a complex master design for the elastomeric replication process.

US2011030808 describes a pulsed laser triggered high speed microfluidic switch and applications in fluorescent activated cell sorting. In certain embodiments this invention describes the pulsed-laser triggered microfluidic switching mechanism that can achieve a switching time of 70 μs. This switching speed is two orders of magnitude shorter than that of the fastest switching mechanism utilized in previous μFACS.

US2015148264 describes a method comprising magnetically holding a bead carrying biological material (e.g., nucleic acid, which may be in the form of DNA fragments or amplified DNA) in a specific location of a substrate, and applying an electric field local to the bead to isolate the biological material or products or byproducts of reactions of the biological material. The document seems describes a device and method in which particle trapping is especially based on magnetic capture.

US2002127736 describes a microfluidic device comprising pumps, valves, and fluid oscillation dampers. In a device employed for sorting, an entity is flowed by the pump along a flow channel through a detection region to a junction. Based upon an identity of the entity determined in the detection region, a waste or collection valve located on opposite branches of the flow channel at the junction are actuated, thereby routing the entity to either a waste pool or a collection pool. The microfluidic device may be formed in a block of elastomer material, with thin membranes of the elastomer material deflectable into the flow channel to provide pump or valve functionality.

Hence, it is an aspect of the invention to provide a (micro) fluidic device (system), which preferably further at least partly obviates one or more of above-

described drawbacks, and which may especially be used at high accuracy, sensitivity and/or selectivity.

In the present application new (micro) fluidic systems are described that can, amongst others, be applied for applications such as pH-gradient chromatofocusing, batch adsorption measurements and adsorption and desorption applications.

Further, especially a particle catch system comprised by the (micro)fluidic device is described that can be applied to catch particles of a predetermined (minimum) size from a first fluid flow (a primary supply flow of particles) and that especially successively may be applied to introduce the caught particle into a second fluid flow, especially a second fluid flow connected to a flow channel system and/or a chamber, especially a flow channel system comprising a chamber to perform a process based on (amongst others) the particles, such as an adsorption/desorption experiment. Herein, especially the chamber is the part of the flow channel system to perform a process wherein a particle is used. The chamber may for instance comprise (a part of) one channel of the flow channel system, either straight or having another shape. The chamber may also comprise a plurality of channels, for instance for circulating a fluid (comprising a particle). The chamber may further comprise one or more valves or restrictions, for instance to block a particle or to circulate a fluid (and a particle) in the chamber.

A characteristic size of a particle may be in the range of smaller than 0.1 μm up to 2.5 mm for the fluidic device (systems) according to present invention. Especially, the characteristic size of a particle in a micro fluidic device (system) as described herein is in the (sub) micrometer (or even nanometer) range, such as in the range of smaller than 0.1–50 μm, such as 1–20 μm. Such a microfluidic device (system), especially, may be incorporated in a chip. The characteristic size may be a diameter. A particle as described herein may comprise a solid particle, such as a glass bead or a resin bead or any a solid material in any other kind of a shape. A particle further may comprise a porous particle. A particle may comprise a synthetic particle. The particle may comprise an inorganic or organic particle. Additionally or alternatively, a particle may comprise a biological cell. A biological cell e.g. may comprise a cancer cell, such as a prostate cancer cell (LNCaP) or a breast cancer cell (MCF-7) (with an average size of the cancer cell that may be 15-16 μm). In embodiments, the particle especially comprises a biological cell. In further embodiments, the particle especially comprises a

solid particle. Especially, the particles may comprise (a mixture of) different types and/or different sizes of particles.

Hence, in a first aspect the invention provides a (micro) fluidic device having a particle trap functionality (a functionality to trap or hold a particle) for a particle in a fluid, the (micro) fluidic device comprising a first fluid flow channel, a second fluid flow channel, and a control channel, wherein the first fluid flow channel is in fluid contact with the second fluid flow channel and intersects the second fluid flow channel at an intersection, wherein the control channel at the location of the intersection is arranged adjacent to the first fluid flow channel separated by a flexible membrane at the intersection, wherein the flexible membrane is configured as a (adjustable) valve, configurable in operation at a first pressure in the control channel in a first position (of the flexible membrane) not to block propagation of a particle of a predetermined (minimum) size through the first fluid flow channel, and at a second pressure in the control channel in a second position (of the flexible membrane) to block propagation of said particle (of a predetermined (minimum) size) through the first fluid flow channel, while in this second position not fully blocking fluid flow in the first fluid flow channel (and allowing a fluid to pass the valve).

The first fluid flow channel may comprise a cross sectional area (perpendicular to a longitudinal axis of the first fluid flow channel). Especially, the (adjustable) valve is configured to provide in the second position (over a length of the valve) a gradual increasing blockade (or obstruction) of the cross sectional area of the first fluid flow channel in a direction parallel to a longitudinal axis of the first fluid flow channel.

The term membrane is especially used in view of the flexibility of the material, especially in a direction perpendicular to the membrane. The membrane *per se* is especially not permeable for particles or liquid (i.e. through the membrane). Hence, the control channel is especially not in fluid contact with the first fluid flow channel or the second fluid flow channel. Hence, a control channel is especially configured to control a (flexible membrane configured as) valve, especially the blocking (and de-blocking) function of the valve.

Especially, the fluidic device comprises a first fluid flow channel and a second fluid flow channel. Especially the first fluid flow channel may have a first channel inlet and a first channel outlet. Also the second fluid flow channel may comprise a second channel inlet and a second channel outlet. Essentially, the first fluid flow channel

intersects the second fluid flow channel at the intersection (especially comprising the valve). Especially the intersection is configured between the first channel inlet and the first channel outlet, and between the second channel inlet and the second channel outlet. Especially, the first fluid channel and the second fluid channel are configure to only allowing a fluid to flow from the first fluid flow channel to the second fluid flow channel (and vice versa) at the intersection. Especially, the intersection does not comprise a Y-configuration, wherein two flows provided from two flow channels enter the intersection (at an upstream side of the intersection) and only one (combined) flow exits the intersection (at a downstream side of the intersection) through one flow channel (or the other way around having one flow channel at the upstream side of the intersection and two flow channels at the downstream side of the intersection).

Especially the first fluid flow channel crosses the second fluid flow channel. Especially the first fluid flow channel crosses the second fluid flow channel. In embodiments, an angle between the first fluid flow channel and the second fluid flow channel (at the intersection) is selected between 30 and 150°. In further embodiments, the angle is selected in the range of 45-135°. Especially, the angle between the first fluid flow channel and the second fluid flow channel at the intersection is selected in the range of 75-105°, such as 80-100°, even more especially in the range of 85 - 95°. Yet in further embodiments, the first fluid flow channel and the second fluid flow channel are configured substantially perpendicular to each other at the location of the intersection. Especially, the first fluid flow channel and the second fluid flow channel are not configured parallel at the intersection. Especially, a first characteristic dimension (such as a width) of the intersection may be equal to a width of the first fluid flow channel. Especially, a second characteristic dimension of the intersection (such as a length) may be equal to a width of the second fluid flow channel.

The (adjustable) valve is essentially configured at the intersection of the first fluid flow channel and the second fluid flow channel. Especially the (adjustable) valve is configured to catch a particle from a flow in the first fluid flow channel, especially to provide said particle to a flow in the second fluid flow channel (see below).

In yet a further aspect, the invention provides a fluidic device having a particle trap functionality for a particle in a fluid, the fluidic device comprising a first fluid flow channel and a control channel, wherein the control channel at a location is arranged adjacent to the first fluid flow channel and separated by a flexible membrane from the

first fluid flow channel, wherein the flexible membrane is configured as a valve, configurable in operation at a first pressure in the control channel in a first position not to block propagation of a particle of a predetermined size in the first fluid flow channel, and at a second pressure in the control channel in a second position to block with said flexible membrane propagation of said particle through the first fluid flow channel, while in this second position not fully blocking fluid flow through the first fluid flow channel. In this way, the valve can be used as valve or stopper to block the particle(s) and to release the particles when desired, for instance for having the particle(s) entrained with a liquid. In such embodiments, the valve may have an upstream side and a downstream side. The valve is thus at least partly configured in the first fluid flow channel, for blocking or not blocking a particle in the first fluid flow channel. Optionally, at a downstream side, the first fluid flow channel may be branched, to provide two or more channel branches, such as a Y-configuration. However, also other configurations are possible, such as the first fluid flow channel having one or more branches downstream from the valve. Hence, over part of its length and width, the control channel is configured adjacent to the first flow channel; this is herein indicated by "at a location". Hence, the invention also provides such fluidic device and a control system, configured to control fluid flow and/or pressure in the first fluid flow channel and fluid flow and/or pressure in the control channel, and optionally also fluid flow and/or pressure in the second fluid flow channel.

Exemplary channel widths in the fluidic device may be in the range of 0.2 μm–10 mm, especially in the range of 0.2–1500 μm, such as 0.5–1500 μm, or 10–1000 μm for a micro fluidic device, and in the range of 1–10 mm for larger fluidic devices. Because a channel height in the fluidic device may be smaller or larger than a channel width, a channel dimension may be defined by the equivalent circular diameter of the channel, wherein the equivalent circular diameter equals $2*\sqrt{}$(cross sectional area of the fluid flow channel/π) (wherein the cross sectional area of the fluid flow channel is the area of an intersection of the fluid flow channel with a plane perpendicular to a channel axis of the fluid flow channel). Especially, a micro fluidic device as described herein is defined as a fluidic device comprising an equivalent circular diameter of the (first and second) fluid channel in the range 0.1–1000 μm, such as 1–750 μm, such as 10–200 μm. The channel width of the first fluid flow channel and the (optional) second fluid

flow channel (and optionally other fluid flow channels connected to the (micro) fluidic device), however, not necessarily have to be equal to each other.

A channel width and a channel height may especially be defined perpendicular to a (longitudinal) channel axis, and may especially be determined along two respective perpendicular lines. The channel width (and other characteristic dimensions), further, may change over the length of a channel. In an embodiment, at a location upstream of the intersection of the first fluid flow channel and of the second fluid flow channel, the channel width of (especially) the first fluid flow channel gradually decreases in the downstream direction, supporting lining up of particles in the first fluid flow channel at a location upstream of the (adjustable) valve.

If (during operation) a flow comprising particles flows in the first fluid flow channel and the flexible membrane is in the first position, then the (adjustable) valve may not block the particles (in the fluid flow). The flexible membrane is especially configured as a valve, more especially as an adjustable valve (opposed to an on/off valve defined as a binary valve with the setting "open" and "closed"). Therefore herein we also may refer to the condition "the membrane is in the first position" as "the (adjustable) valve in the first position", or we may refer to "the (adjustable) valve in the second position" if the membrane is in the second position. Moreover, the membrane may be in the first position if the pressure in the control channel is at the first pressure, and the membrane may be in the second position if the pressure in the control channel is at the second pressure. Hence, the terms "first pressure in the control channel", "first position of the membrane", and "first position of the (adjustable) valve" all refer to the same stage and may be used interchangeably herein referring to the same stage ("the membrane in the first position"). Moreover, also the terms "second pressure in the control channel", "second position of the membrane", and "second position of the (adjustable) valve" refer to the same operating condition or operating stage and these terms may also be used interchangeably herein.

In the first position of the (adjustable) valve, the valve, especially is configured substantially not to block the first fluid flow channel. Thus, in the first position of the (adjustable) valve all particles comprised in a fluid flowing in the first fluid flow channel may not be blocked by the (adjustable) valve and may pass the valve. In the second position of the (adjustable) valve, the valve, especially may block a part of (the initial passageway of) the first fluid flow channel. Consequently a particle of a specific

(minimum) size that flows (with a fluid) in the first fluid flow channel may be blocked by the (adjustable) valve in the second position, whereas a particle of a size smaller than that specific size may not be blocked by the (adjustable) valve in the same second position and may pass the valve during operation.

The (adjustable) valve in the second position especially is configured to trap a particle of a specific (predetermined) (minimum) size while never completely blocking the first fluid flow channel (a particle trapped in the valve in the second position potentially, however, may (in combination with the valve) block any further fluid flow through the valve). It was found that this behavior could be realized by a valve comprising a funnel-type shape or v-type shape, i.e. a shape wherein in the second position of the membrane, the (adjustable) valve substantially does not block the "cross sectional area" (i.e. the inner area of a cross section of the first fluid flow channel perpendicular to a longitudinal axis of the first fluid flow channel) of the first fluid flow channel at the upstream side of the valve, whereas the blockade of the cross sectional area of the first fluid flow channel (in the valve) provided by the (adjustable) valve gradually increases from the upstream side of the valve in the direction towards the downstream side of the valve at least over a part of the length of the valve (that is, the distance between the downstream side of the valve and the upstream side of the valve).

The v-type valve may especially comprise a symmetry plane comprising a longitudinal (center) axis of the first fluid flow channel. Especially in the second position, the v-type shaped valve may comprise a tapered shape, tapering from the upstream side of the valve towards a further location of (or in) the valve (a location of/in the valve downstream with respect to the upstream location). Especially the v-type valve may comprise a conical shape (especially in the second position). The membrane may comprise a substantially flat membrane (shape), especially in the first position. Additionally or alternatively, the membrane may comprise a parabolic shape, especially in a longitudinal direction of the first fluid flow channel, especially in the second position. The membrane may also comprise a substantially flat membrane (shape) in the second position. Consequently, in said (funneling, tapering and/or conical) part of the length of the valve the effective passageway area gradually decreases. The effective passageway area (at a specific location) may be defined as the part of the cross sectional area (of the first fluid flow channel, see above) at the respective location of the (adjustable) valve that is not blocked by the valve. Optionally, the blockade of the

cross sectional area of the first fluid flow channel may decrease again (the passageway may increase again) at the side of the valve opposite to the upstream side of the valve (for instance if the V-shape is part of an hourglass shape). However, the (adjustable) valve, especially is configured to provide the gradual increasing blockade of the cross sectional area (perpendicular to a longitudinal axis of the first fluid flow channel, see above) of the first fluid flow channel in a direction parallel to a longitudinal axis of the first fluid flow channel (especially, in the (designed) flow direction of a fluid flow through the first fluid flow channel during operation of the (micro) fluidic device). Herein, an effective passageway area at a specific location in a fluid channel may in general also be defined by the smallest inner area of a plane intersecting the fluid flow channel perpendicular to a channel axis. At an increased pressure in the control channel (in the second position), the membrane (in the valve) may be "lifted" or "actuated" at a location, especially (temporarily, especially reversible) decreasing the cross sectional area (of the first fluid flow channel) at said location. Especially, the effective passageway area at a location of the valve comprises the cross sectional area of the first fluid flow channel (perpendicular to a longitudinal axis of the first fluid flow channel) at that location. Hence, a blockade or obstruction of the cross sectional area (at a location) as described herein may relate to (reversible) change (a reduction) of the cross sectional area (at said location). The fluidic device may be configured to comprise a plurality of second positions (of the membrane), in dependence of the pressure in the control channel. In this way the particle size of particles passing or not passing the valve (or particle trap) may be controlled. Hence, the membrane may be configurable in a plurality of positions. Hence, the valve is configurable in a position providing a larger cross-sectional area and a position with a smaller cross-sectional area

Hence, in an embodiment, the invention provides the (micro) fluidic device, wherein the first fluid flow channel at a location of the valve comprises an effective passageway area, wherein in the second position (of the membrane) a first effective passageway area at the upstream side of the valve is larger than a second effective passageway area at a location further downstream from the first effective passageway area and wherein the second effective passageway area is larger than zero. Especially, the fluidic device in the second position is configured to comprise a larger cross sectional area of the first fluid flow channel at the upstream side of the (adjustable)

valve than at a location further downstream (of the upstream side) in the (adjustable) valve.

Hence the valve may be configured to provide a cross sectional area (of the first fluid flow channel), wherein the cross sectional area decreases along at least part of the channel axis from the upstream side of the valve towards the downstream side of the valve, especially wherein the cross sectional area is larger than zero. Especially a minimal cross sectional area is larger than zero allowing a fluid to flow through the valve. Especially the minimal cross sectional area is smaller than (pre)determined size of a particle (to trap in the valve).

A funnel type, v-type shape, conical or tapered configuration of the (adjustable) valve as described herein may especially be defined by its geometry. The v-type shaped (adjustable) valve comprises a first wall comprising the membrane adjacent to the control channel, a valve width especially equal to the width of the (first) fluid flow channel, a first valve section comprising a first valve section length (especially measured along a line parallel to the longitudinal axis of the first fluid flow channel) and comprising the upstream side of the valve, and a second valve section, comprising a second valve section length (especially measured along a line parallel to the longitudinal axis of the first fluid flow channel and comprising the downstream side of the valve, wherein the v-type valve comprises a valve length, being equal to the distance between the downstream side of the valve and the upstream side of the valve, and also being equal the total of the first valve section length and the second valve section length. Especially, only in the second valve section, the membrane comprises substantially the complete width of the v-type shaped (adjustable) valve (especially) being the width of the (first) fluid flow channel at the intersection), whereas in the first valve section, only a fraction of the valve width (i.e. the width of the (first) fluid flow channel at the intersection) is comprised by the membrane. The second valve section length may be larger than the first valve section length, such as two or four times as large. However, the second valve section length, especially, is substantially equal to or smaller than the first valve section length. The second valve section length, further may be larger than the width of the valve (the width of the first fluid flow channel at the intersection). However, the length of the second valve section is especially smaller than the width of the valve (or the width of the first fluid flow channel at the intersection). The ratio of the length of the second valve section to the width of the valve may for

instance be in the range of 0.05–0.95, such as 0.1–0.9, such as 0.1–0.6, depending for instance on the flexibility of the membrane, the applied pressure in the control channel (see below) and the length of the first valve section, and the width of the (first) fluid channel. Especially, when the second valve section length (in relation to the width of the valve) is too small, the valve in the second position may not block the first fluid flow channel to such an extent that a particle may be blocked and the valve, also, may become too weak. However, if the second section length is too large, the valve may completely block the first fluid flow channel in the second position. (It is noted that a "normal" on/off valve–see below–is provided if the second section length is configured to be equal to the valve length). Hence the valve, and therefore also the first section length and the second section length should be configured to enable to block a particle in the second position, while at the same time essentially not completely blocking a fluid flow in the first fluid channel. Especially, the first section length and the second section length are selected to provide a minimum cross sectional area in the second position of the valve that is essentially larger than zero.

Especially, a funnel-type or v-type shape configuration of the (adjustable) valve provides robustness and strength to (the membrane) of the valve. A v-type shape valve may generate a focused flow in the center of the channel. In contrast to e.g. a sieve valve, this flow may stop when a particle having substantially the same size as the (controllable) area of the opening is captured, preventing extra particles from flowing in and being trapped in the valve. The trapping of a particle in the center position of a first flow (by the v-type shaped configuration), may further be advantageous because it allows improved control over the particle when it is introduced into the second fluid flow channel (see below). The valve may especially comprise a small volume, especially requiring only a small fluid flow to provide a caught particle in the second fluid flow channel. Yet another advantage of the funnel type shape is that irregular particles, such as broken particles, especially particles that preferably are not caught, because of a deviating dimension, may be oriented in the fluid flow in the funnel and pass the (adjustable) valve.

The membrane is configured to comprise a specific strength and flexibility, wherein the strength and flexibility may be provided by the material comprised in the membrane and also by the thickness of the membrane and wherein the required strength and flexibility may depend on the cross section of the fluid flow channel. Especially,

for instance a thick membrane may not be flexible enough to provide a small enough effective passageway area to block a particle of a predetermined size in a fluid flow channel comprising a (relatively) small cross sectional area, whereas a thin membrane may be too flexible and may provide an uncontrollable valve that may collapse in a fluid flow channel comprising a relatively large cross sectional area. The (adjustable) valve especially is flexible, wherein it may comprise of elastomeric polymers, such as, polydimethylsiloxane, polyisoprene, polybutadiene, poly(styrene-butadienestyrene), polychloroprene, polyisobutylene, polysulfone, polyurethanes, polytetrafluoroethylene, cyclic olefin copolymer, polyimide, especially the valve comprises polydimethylsiloxane.

Especially, the (adjustable) valve is operated by the pressure in the control channel. The pressure may be provided by any fluid. In an embodiment, the pressure is provided by a gas, such as air or nitrogen, and the valve comprises a pneumatically controlled valve. In another embodiment, the pressure may be provided by a liquid, such as water or oil, wherein the adjustable valve may comprise a hydraulically controlled valve. The pressure in the control channel is e.g. selected from the range of 1–10 bar (absolute), such as 1–5, especially 1–3 bar (absolute). However, pressures below ambient pressure may optionally also be applied. In further embodiments, the pressure difference between the pressure in the control channel and the pressure in the fluid flow channel is selected from the range of 0–10 bar, such as 0–5, especially 0–2 bar. Especially, the pressure difference may be 0 bar for an open valve, especially for a valve comprising a membrane not blocking the fluid flow channel. The term “control channel” may in embodiments also refer to a plurality of control channels. In yet further embodiments, the pressure in two or more control channels may be controlled at different pressures.

It further may be advantageous to adjust the (adjustable) valve position or setting (the degree of blockage) of the (adjustable) valve, to allow control over (the size of) the particles that are blocked by the (adjustable) valve. Hence, in a further embodiment, the invention provides the (micro) fluidic device, having a controllable pressure in the control channel, such as a continuously controllable pressure (and thus continuously controllable passage dimension). In embodiments, the (micro) fluidic device is configured to provide the second passageway area by controlling the first pressure in the control channel. Especially, the fluidic device is configured to comprise a first cross

sectional area (of the first fluid flow channel) at a location (of the valve) at an initial pressure in the control channel that is larger than a second cross sectional area (of the first fluid flow channel) at said same location (in the valve) at an other pressure in the control channel, if the other pressure is larger than the initial pressure. Especially, the cross sectional area of the first fluid flow channel at the intersection may essentially always be larger than zero. Especially, the effective passageway area in the (adjustable) valve may decrease at increasing pressures and the (adjustable) valve may further be opened by decreasing the pressure in the control channel. Hence in yet a further embodiment, the second effective passageway area at a first pressure in the control channel is larger than the second effective passageway area at a second pressure in the control channel if the second pressure is larger than the first pressure. Especially, the pressure may be increased or decreased in a continuous way providing a (second) effective passageway area that also may be continuously set between a minimum value (at a maximum value for the second pressure) and a maximum value (wherein for the maximum value of the effective passageway area, the pressure is set at the first pressure and the cross sectional area of the fluid flow channel substantially may not be blocked). Especially, the fluidic device may be configured to comprise an effective passageway area at an initial (second) pressure in the control channel being larger than the effective passageway area at a further (second) pressure, wherein the effective passageway area is at a location of the valve remote from the upstream side of the valve, and wherein the further (second) pressure is higher than the initial (second) pressure. Especially, the fluidic device may be configured to provide a minimal cross sectional area of the first fluid flow channel at the intersection as a function of the pressure in the control channel. Especially, the minimum cross sectional area (of the first fluid flow channel at a location at the intersection) may be inversely proportional to the pressure in the control panel. Hence, the fluidic device may be configured to providing the valve, especially the membrane in a plurality of positions as a function of the pressure in the control channel.

The fluidic device, especially the adjustable valve, may be configured to comprise an effective passageway (of the first fluid flow channel) or a cross sectional area of the first fluid flow channel (at the intersection) as a function of the pressure in the control channel. Hence, the fluidic device may also be functionally coupled to a pressure unit, configured to control pressure (of the fluid) in the control channel. For

instance, the fluidic device may be comprised by a larger system. To control the pressure in the control channel, a pump may be applied; further, also one or more valves may be applied to control the pressure in the control channel. The term "pump" herein may also refer to a plurality of pumps (which may independently controlled). The pump may (also) be selected from the group consisting of a rotary pump, a syringe pump, and a peristaltic pump. The pressure(s) in the control channel may (also) be controlled by the control system, such as by controlling the pump and one or more valves. Note that, such as due to the presence of the valve(s) in the control channel, the pressure in the control channel may vary over the control channel. Further, as also elsewhere indicated herein, the term control channel may optionally also refer to a plurality of control channels. The pressure in all control channels may be controlled by the control system.

The invention, further provides, the (micro) fluidic device to allow catching a particle from a fluid flow in the first fluid flow channel, trapping the particle in the (adjustable) valve of the (micro) fluidic device and successively releasing the particle in a second fluid flow channel, especially wherein the second fluid flow channel is connected to (a further channel system comprising) a chamber to introduce the particle in said chamber (to perform a process wherein the particle is used).

It may further be beneficial if the flow in the first fluid flow channel and the flow in the second fluid flow channel may be controlled (independently) when trapping a particle in the (adjustable) valve. Especially, (independent) control over the flow of fluids in the first and second fluid flow channel is advantageous if the particle after trapping successively may be introduced in the second fluid flow channel. In an embodiment, the flow in the first fluid flow channel for instance is controlled by a pump or another fluid flow support system (herein also indicated as pressure unit). In another embodiment, the flow in the first fluid flow channel may be controlled by a (channel) valve provided in the first fluid flow channel; said valve referred herein as a channel valve to distinguish the channel valve from the (adjustable) valve or v-valve, configured in the first fluid flow channel and/or configured at the intersection of the two fluid flow channels (i.e., the first fluid flow channel and the second fluid flow channel). In an embodiment, the flow especially may be controlled by providing a channel valve arranged upstream of the intersection of the first fluid flow channel and the second fluid flow channel and a channel valve arranged downstream of the

intersection (of the first fluid flow channel and the second fluid flow channel). The channel valves may be provided to control the flow in the (first and/or second) fluid flow channel, especially to enable a fluid flow in the (first and/or second) fluid flow channel or to disable or block a fluid flow in the (first and/or second) fluid flow channel. For this functionality, the channel valves may be configured in several ways. In an embodiment, both channel valves in each of the respective fluid flow channels may be configured as an on/off valve having a first condition (of the valve) blocking the fluid flow (in the respective fluid flow channel) and a second condition (of the valve) allowing fluid to pass (and continue flowing through the valve and in the respective fluid flow channel). Herein, "on/off valves" may also be referred to as "shut-off valves", "push-up shut-off valves" and "binary valves". Also, in another embodiment, one of the valves (of the set of valves per fluid flow channel), especially the valve at the downstream side of the intersection (of the first fluid flow channel and the second fluid flow channel) may be configured as a check valve or one-way valve allowing a fluid to flow (in the respective fluid flow channel) in one direction and blocking the fluid flow (in the respective fluid flow channel) in the opposite direction, whereas the other channel valve (in the respective fluid flow channel) is configured as an on/off valve. In a specific embodiment, the channel valve(s) upstream of the intersection (of the first fluid flow channel and the second fluid flow channel) and the channel valve(s) downstream of the intersection (of the first fluid flow channel and the second fluid flow channel) especially are configured as a (channel) valve comprising a first condition allowing fluid to pass and a second condition disabling fluid flow in the channel valve. Different types of valves comprising above mentioned functionalities are known in the art. In an embodiment (one of) the channel valve comprises a magnetic valve, in another embodiment, (one of) the channel valve(s) comprises a pneumatic valve. Yet, in another embodiment (one of) the channel valve(s) comprises a hydraulic valve. Also check valves are known in the art. Combinations of different types of (channel) valves may be applied.

Hence, in a specific embodiment, the invention further provides the (micro) fluidic device, wherein further two first channel valves are provided in the first fluid flow channel and two second channel valves are provided in the second fluid flow channel, wherein the two first channel valves are each provided at opposite sides of the intersection (of the first fluid flow channel and the second fluid flow channel)

configured to allow complete blockage of the first fluid flow channel at both sides of the intersection (of the first fluid flow channel and the second fluid flow channel) and the two second channel valves are each provided at the opposite site of the intersection (of the first fluid flow channel and the second fluid flow channel) configured to allow complete blockage of the second fluid flow channel at both sides of the intersection (of the first fluid flow channel and the second fluid flow channel), and wherein during operation a fluid flow in the first and second fluid flow channels can be controlled (independently from each other) by controlling the first and second channel valves.

Especially, a (micro) fluidic device comprising an adjustable valve provided at the intersection of a first fluid flow channel and a second fluid flow channel, wherein each fluid flow channel comprises a channel valve upstream of the intersection (of the first fluid flow channel and the second fluid flow channel) and a channel valve downstream of the intersection (of the first fluid flow channel and the second fluid flow channel) may be applied to catch a particle comprised in a fluid flow flowing in the first fluid flow channel and, successively, to introduce the particle in a fluid flow flowing in the second fluid flow channel. A particle of a specific (minimum) size, especially may be caught from a fluid flow comprising said particle flowing in the first fluid flow channel comprising the two (first) channel valves providing a condition not blocking the fluid flow (in the first fluid flow channel), wherein the adjustable valve comprises the second condition (by providing the second pressure in the control channel) and wherein the (second) channel valves in the second fluid flow channel comprise a condition completely blocking the fluid flow in the second fluid flow channel. Successively, the (trapped) particle may be introduced in the second fluid flow channel by providing the first channel valves in the condition completely blocking the fluid flow in the first fluid flow channel, and providing the second channel valves in the condition not blocking the fluid flow in the second fluid flow channel and providing the adjustable valve in the first position (by providing the first pressure in the control channel) to release the particle in the second fluid flow channel. Especially, the amount (the volume or flux) of fluid flowing in the second fluid flow channel required for introduction of the trapped particle in the second fluid flow channel may be proportional to a volume of the intersection (valve). Also a time required to introduce the trapped particle in the second fluid flow channel may be proportional to said

volume. Hence the valve and the intersection of the first fluid flow channel and the second fluid flow channel especially may be configured to minimize said volume.

Especially a fluidic device comprising an adjustable valve in a first fluid flow channel may be applied to catch one or more particle(s) and successively release the particles(s) again, especially in the first fluid flow channel. Especially, after releasing the particle(s), channel valves configured downstream of the fluidic device may be controlled in such a way that the released particle(s) may be directed into a further fluid flow channel configured downstream of the fluidic device, or especially into one of the channel branches (especially both comprising a channel valve) when the first fluid flow channel is configured as a Y-configuration downstream form the valve. In an embodiment, at least one fluid comprises a liquid. In a further embodiment, at least one fluid comprises a gas. In an embodiment, a fluid is a liquid and another fluid is a gas. Yet in another embodiment, all fluids comprise a liquid. The term "fluid" may also refer to a combination of different fluids. In yet further embodiments, the term fluid may refer two or more immiscible liquids. In even further embodiments, the fluid may refer to a liquid and a gas dispersed in the liquid. The first flow channel and optional second flow channel may especially be configured (and used) to host a liquid; the control channel may especially be configured (and used) to host a gas.

In an embodiment, the invention further provides a control system, (functionally) connected to the fluidic device, wherein the control system is configured to control the conditions of the (adjustable and channel) valves. In a further embodiment, the invention further comprises a detection system to detect the presence of a particle trapped at the intersection of the first fluid flow channel and the second fluid flow channel (and/or optionally elsewhere in the fluidic device, such as in the second flow channel, downstream from the intersection). In an embodiment the detection is based on optical analysis, such as by using a (CCD) camera. In another embodiment the detection is based on a pressure difference measured over the adjustable valve. In a further embodiment the detection is based on the electrical impedance over the fluidic channel that passes through the adjustable valve. In yet another embodiment, the detection is based on an analysis of (reflection or absorbance of) electromagnetic waves at the intersection of the first fluid flow channel and the second fluid flow channel. In a further embodiment the detection system is linked to the control system and the conditions of the valves are set based on presence of a trapped particle. The detection

system may be configured to count the particles. Hence, in this way an exact number of particles (of a specific size) may pass the particle trap. Particle counting may especially be done at the intersection, but may alternatively or additionally also be done elsewhere in the fluidic device, or processing device.

In a further embodiment, an introduction system is connected to the fluidic device, especially to the first fluid flow channel, wherein the introduction system is configured to provide a fluid flow with one or more particles into the first fluid flow channel. Many different introduction systems such as all kinds of pumps known in the art may be configured for this purpose. In an embodiment, the introduction system comprises a pump selected from the group consisting of a rotary pump, a syringe pump, and a peristaltic pump. In another embodiment the introduction system comprises a pumping system comprising a pressure regulator. In a further embodiment, the introduction system is (also) functionally connected to the control system. Coupling the introduction system to the control system may especially be advantageous to control the flow in the first fluid flow channel, e.g. to stop the fluid flow in the first fluid flow channel based on the presence of a particle at the intersection of the first fluid flow channel and the second fluid flow channel, or to speed up or slow down the fluid flow in the first fluid flow channel. The introduction system may be configured to provide a diluted flow with one or more particles.

Especially, the second fluid flow channel may be connected to a system further downstream of the adjustable valve, such a channel system or a chamber, especially a channel system comprising a chamber or even more especially a plurality of parallel channel systems, especially (each) comprising a chamber, for performing a process (or–simultaneously–multiple parallel processes) comprising the particle(s) introduced in chamber. Examples of processes are (batch) adsorption/desorption equilibrium experiments for generating essential information on the distribution of chemicals or bio-materials over a solid and a fluid phase; (dynamic) separation (chromatography) and purification of industrial (bio)chemicals; sample enrichment, especially using resins with a high binding capacity, with the aim to improve detection or determination of analytes; diagnostics (detecting analytes or biomarkers in a medical-clinical, environmental or other sample), catalyzed chemical reactions, etc.. Especially, for comparative studies or for instance for said batch adsorption experiments it may be advantageous to perform multiple processes simultaneously, by only changing one (or a

few) experimental parameters (such as a specific concentration in adsorption experiments) while keeping the other parameters constant, and hence to apply a system comprising a plurality of parallel channel systems–comprising a chamber, see also below). Especially, the system may comprise controlling elements to control the process(es), such as a temperature controlling element, a flow system to circulate fluid (with or without particles) in the system (such as in the channel system(s) and/or chamber(s)) and/or refresh the fluid, a holding system for arranging a column of particles (a packed bed or e.g. a chromatography column), and analyzing elements such as a conductivity analyzer, a pH meter, a flow meter, fluorescence detection, and a temperature indicator, etc.. Herein, the terms "to circulate", "circulating", etc. may refer to a (continuous) circulating flow in one direction of flow. It may also refer to a back and forth flow in a flow channel with at least a partial loop shape. The system further may comprise a device or option to connect to a (sensitive) analytical instrument, such as a mass spectrometer and/or an ultraviolet-visible spectrometer, a fluorescence spectrometer, and an electrochemical measuring cell. Different solutions are known in the art to connect to an analytical device. The system may comprise a flow channel (system) to connect to an analytical device. The system may e.g. also comprise a flow channel comprising a transport means and/or valve systems for (allowing) transport of a fluid to be analyzed to an analytical device. Or the system may comprise other options to transport a sample to an analytical device.

In another aspect, the invention provides a processing device comprising the (micro) fluidic device as defined herein, an introduction system configured to provide a fluid flow with one or more particles into the first fluid flow channel (of the (micro) fluidic device), a flow channel system, in fluid contact with the second fluid flow channel (of the (micro) fluidic device), comprising a chamber configured for performing a process wherein a particle is used, wherein the process may especially be selected from a chemical process, a biochemical process, a physical process, and an analytical process, optionally an analysis system configured to analyze a parameter of the process, and optionally a detection system configured to detect a presence of a particle at the intersection of the first fluid flow channel and the second fluid flow channel (and/or optionally elsewhere in the fluidic device), and a control system at least configured to control the fluidic device and the introduction system. The analysis system may be integrated with the fluidic device, or with the processing device, but

may optionally also be configured external of the fluidic device or processing device. In an embodiment the processing device is configured to circulate a particle (in a fluid) in the flow channel system and/or the chamber. Hence, the processing device may comprise particles, especially a column of particles, especially in the channel system and/or the chamber. In a further embodiment, the processing device may be configured to provide a column of particles in the channels system and/or the chamber. In yet another embodiment the processing device is configured to enable a flow of particles in the flow channel and/or the chamber and to enable to hold a particle at a specific location in the flow channel system and/or chamber (to provide e.g. a column of particles). The fluidic device is especially integrated in a chip. Likewise, the processing device is especially integrated in a chip. Hence, both devices are herein also indicated as microfluidic devices.

The invention also provides a processing device comprising a plurality of (micro) fluidic devices as defined herein, an introduction system configured to provide a fluid flow with one or more particles into the first fluid flow channel of a first (micro) fluidic device, a flow channel system, in fluid contact with the second fluid flow channel of the first (micro) fluidic device), comprising a chamber configured for performing a process wherein a particle is used, wherein the process may especially be selected from a chemical process, a biochemical process, a physical process, and an analytical process, optionally an analysis system configured to analyze a parameter of the process, and optionally a detection system configured to detect a presence of a particle at the intersection of the first fluid flow channel of the first (micro) fluidic device and the second fluid flow channel (and/or optionally elsewhere in the fluidic device), and a control system at least configured to control the fluidic devices and the introduction system, wherein a second and optionally further (micro) fluidic devices are configured downstream of the first (micro) fluidic device, and wherein especially each first fluid flow channel of a (micro) fluidic device configured downstream of another (micro) fluidic device is functionally coupled with the second fluid flow channel of such upstream configured other (micro) fluidic device. In this way, mixtures of particles of different sizes may be separated into one or more fractions with a relatively homogeneous particle size distribution. Hence, the invention also provides a chip comprising a plurality of fluidic devices which are functionally coupled to each other.

In an embodiment, the invention provides a chip comprising (part of the) the processing device, wherein the processing device comprises the (micro fluidic) device configured as a micro fluidic device (comprising a first fluid flow channel and a second fluid flow channel, especially comprising a characteristic channel dimensions (width) selected in the range of 0.2–1500 μm). In another embodiment, the processing device comprises larger channel dimensions, and the processing device may not be comprised in a chip. Especially, the processing device comprising the (micro) fluidic device described herein may be scaled to the desired dimensions of the particles, such as beads, but also biological cells or nano-particles. Even differently sized particles may be introduced in the same channel system. Hence in an embodiment, the invention provides a processing device wherein nano-particles and biological cells are introduced in the flow channel system allowing for instance to screen for effects of nano-particles (nm scale) on biological cells (μm scale). Further, the fluidic device may be comprised by a chip but one or more elements of the processing device may not be comprised by this chip. In a further embodiment the processing device comprises at least two fluidic devices. In an embodiment the processing device comprises a first fluidic device and a second fluidic device, wherein the first fluidic device is configured to load nano-particles in the flow channel system and the second fluidic device is configured to load biological cells in the channel system.

Often, for instance for research and development purposes many of the processes wherein a particle is used, such as a chemical process, a biochemical process, a physical process, and an analytical process, preferably a set of experiments (processes) under substantially the same condition are performed, wherein only one or two parameters are changed. For these processes, it may be very advantageous to perform the processes parallel and at the same time in the same environment and therefore in a process device comprising a plurality of (similar) flow channel systems, like 2-256, such as 4-128 flow channel systems.

It may further, especially be advantageous to introduce the desired particle(s) in each flow channel system by one or more, especially one, fluidic device and introduction system as described herein. However, it may also be advantageous to introduce the desired particle(s) in each flow channel by more than one fluidic device and at least one introduction system. Especially, by functionally coupling each flow channel system with the one fluidic device (and one introduction system), the one

fluidic device may be applied to sequentially load a particle in each flow channel system, especially to efficiently make use of the equipment, the reagents and the other starting material. Especially, by providing a fluidic device to each flow channel system, the fluidic devices may be used to load a particle in each flow channel simultaneously. It further may be advantageous also to configure an analysis system to analyze a parameter of each of the processes in each of the flow channel systems. The invention, therefore, also provides a processing device comprising the (micro) fluidic device as defined herein, an introduction system configured to provide a fluid flow with one or more particles into the first fluid flow channel (of the (micro) fluidic device), a plurality of (similar) flow channel systems in fluid contact with the second fluid flow channel (of the (micro) fluidic device), (especially) each comprising a chamber, especially in parallel arranged flow channel systems, configured for performing a process wherein a particle is used, wherein the process is selected from a chemical process, a biochemical process, physical process, and an analytical process, optionally an analysis system configured to analyze a parameter of (each of) the process(es), and optionally a detection system configured to detect a presence of a particle at the intersection of the first fluid flow channel and the second fluid flow channel, and a control system at least configured to control the fluidic device and the introduction system, especially wherein the fluidic device and the plurality flow channel systems is comprised by a chip.

Hence, the invention also provides a processing device comprising a plurality of (in parallel arranged) flow channel systems in fluid contact with the second fluid flow channel, wherein the processing device further comprises a second fluid flow direction system, comprising (e.g.) a set of valves, configured to control the fluid flow (comprising one or more particles) in the second fluid flow channel to (either one of) each of the plurality of flow channel systems. The second fluid flow direction system may comprise a set of valves, especially on/off valves, wherein each valve may block propagation of the fluid flowing in the second fluid flow channel to a specific fluid flow channel system, or may enable a flow into the specific flow channel system, therewith enabling loading one or more particles in a specific flow channel system, especially sequentially loading one or more particles in each of the plurality of flow channel systems. Especially, in such a system parallel experiments may be performed applying only one fluidic device, and preferably also (only) one analyses system, one

detection system, one introduction system, and one control system (especially also configured to control the second fluid flow direction system).

In a further embodiment, the processing device comprises at least one pair of flow channel systems, wherein each pair of flow channel systems comprises a first flow channel system comprising a first chamber and a second flow channel system comprising a second chamber, wherein the first chamber and the second chamber comprise substantially the same dimensions and substantially the same physical parameters, and wherein each first flow channel system is in fluid contact with a fluidic device configured to load a particle in the first flow channel system. Especially, such an embodiment may be advantageously used for determining an effect of a particle on a process wherein the particle is used, by analyzing a parameter of the process in (each of) the first chamber(s) (or first channel system(s)) and comparing the parameter with the value obtained from analyzing the parameter in (each of) the second chamber(s) (or second channel system(s)) comprised in the pair of flow channel systems. Hence, especially the second chamber (or second channel system) may provide a reference value of the parameter for the first chamber (or first channel system) of the pair of channel systems. Such an embodiment may be efficiently applied, especially by selecting the number of particles loaded in each of the first chambers different from each other.

In an embodiment, the processing device, especially the flow channel system(s), comprise(s) at least one further fluid flow channel (for supplying further fluids to the processing device, or withdrawing fluid from the flow channel device), wherein a further fluid flow channel also may comprise a valve, especially a (channel) valve comprising a (first) condition not blocking the fluid flow (in the further fluid flow channel) and a (second) condition completely blocking the fluid flow in the further fluid flow channel.

In a further embodiment, the invention provides a processing device comprising the (micro) fluidic device, especially the processing device comprises fluids that are moved, mixed, separated, reacted, or otherwise processed, wherein the fluids may comprise liquids and/or gasses, especially the fluids may comprise liquids flowing in a fluid flow channel (and flow channel system).

In a specific embodiment, during operations the (micro) fluidic device is controlled (manually or by the control system) to load a particle in (one of) the flow

channel system(s). In embodiments the processing device comprises a detection system, and the fluidic device is configured to load a particle in (one or more of) the flow channel system(s), especially when a particle is detected by the detection system. In a further embodiment the processing device comprises a detection system, and the fluidic device is controlled to load the particle in (one or more of) the flow channel system(s) when a particle is detected by the detection system. Hence, in embodiments, the processing device, during operation the fluidic device, is controllable to load a particle in the flow channel system. Especially the fluidic device is configured to load a particle in the flow channel system (during operation), especially when a particle is detected by the detection system. Hence, in embodiments the processing device comprises a detection system, wherein the fluidic device is configured to load a particle in the flow channel system. Especially, the detection device may detect the presence of a particle (trapped) at the intersection of the first fluid flow channel and the second fluidic channel of the (micro) fluidic device during operation. In a specific embodiment, the detection system is connected to the control system, wherein the control system comprises a unit to count the number of particles when detected by the detection system. In another embodiment, the detection system comprises a counting unit. Yet in another embodiment the processing device further comprises a (separate) counting device and the counting device is connected to the detection system (and optionally connected to the control system). In a further embodiment, the control system is configured to prevent the processing device from loading particles when a predetermined number of particles are loaded in the flow channel system(s), or from loading particles in specific flow channel system if a plurality of is used. In yet another embodiment, the number of loaded particles (per flow channel system) is indicated at a display and the loading of particles in the flow channel system is stopped manually after loading a predetermined number of particles. Hence in a further embodiment the invention provides the processing device, wherein a predetermined number of particles are loaded in the flow channel system.

The loaded particles may be used for a process comprising the particles, such as for an adsorption/desorption experiment, a separation process (such as chromatography), a purification process, a toxicity screening, a chemical (catalyzed) reaction, a biological cell study (such as a drug dose repose study on a biological cell, a binding kinetic study on RNA, DNA, and anti-bodies, studies on the adsorption of

molecules on artificial tissues and organs, studies on solid-phase immunoassays, immuno-magnetic cell separations, immobilized enzymes, and biosensors), etc.. Especially, the effect of operating conditions, such as type of particles, particle porosity, pore size distribution, total (effective internal/external) surface area of the particles, ligand density and ligand distribution, pH, salt concentration, temperature, protein concentration, concentration of a reactant, residence time, etc. may be studied using the processing device described herein. The processing device, further may be applied for instance in clinical, forensic, and environmental analysis such as by adsorption of contaminants analytes and biomarkers, or catching biologic cells, such as a prostate cancer cell (LNCaP) or a breast cancer cell (MCF-7) to perform a clinical trial. The processing device, further, especially may be applied for gaining relevant data for the design of dynamic separation processes (chromatography). The processing device may be applied for batch wise processes wherein a fluid circulates in the flow channel system (and the chamber) during a processing period and the particles are circulated with the fluid during substantially processing period or the particles may be stagnant (providing e.g. column) during at least part of processing period. In a further embodiment (fresh) fluid may be fed to the flow channel system (and the chamber) and withdrawn from the system after a specific period of time. The processing device further may also be applied for continuous processes wherein continuously a fluid flow is provided to the processing device to interact with the particles and successively exit the processing device again.

For some of the processes it may be advantageous to perform the process on particles configured to provide a column or packed bed (reactor). Hence, in a specific embodiment, a number of particles are loaded in the flow channel system/chamber and wherein the number of particles provides a column comprising particles configured for performing the process. Hence, in embodiments, the processing device comprises a number of particles loaded in the in the chamber, wherein the number of particles provide a column comprising particles configured for performing a process. For some processes, however, it may also be advantageous to have the particles in the flow channel system not contacting each other, to increase the effective (open for interaction with –a component in the– fluid) surface area of the particles. Especially, for performing adsorption/desorption experiments it may be advantageous to have a large and known surface area, and circulate the fluid with the particles in the flow channel

system instead of providing a column (wherein the effective surface area may be decreased because of contacting particles) comprising the particles. Hence in an embodiment, a number of particles are loaded in the flow channel system and the number of particles are circulated in the flow channel system. In an embodiment, a selected number of particles may be (first) loaded in the second fluid flow channel or in a further flow channel providing a column of the selected number of particles. Especially, the selected number of particles may successively be directed to a flow channel system and wherein the number of particles are circulated in the flow channel system.

Especially, the processing device comprises the (micro) fluidic device in fluid connection with at least one flow channel system, wherein especially in the flow channel system(s) (comprising a chamber) a process using a particle may be performed. The flow channel system(s) (and the chamber) may be configured for many different processes. In a specific embodiment the processing device is comprised in a chip and comprises a micro fluidic device as described herein, wherein the processing device is in fluid connection with at least one flow channel system and at least one further fluid flow channel and wherein the flow channel system(s) comprising the chamber further comprise(s) a set of (further) valves configured as a pump allowing to force a fluid to flow in the flow channel system wherein the direction of flow may be controlled by the set of (further) valves. Especially, such an embodiment is advantageous for performing experiments, for instance comprising the steps (i) loading a number of particles in the chamber(s) providing a column (in each chamber), (ii) loading a (protein) solution in the flow channel system(s) by controlling the condition of the channel valve(s) and the set of further valves configured as a pump (and analyzing a characteristic parameter of the (protein) solution before the experiment), (iii) forcing the (protein) solution to flow over the column (by controlling the set of further valves configures as a pump) (and allowing part of the (protein) solution to adsorb at the surface of the number of particles), (iv) loading a new solution in the flow channel system whereby the (protein) solution is forced out of the processing device, and optionally (v) analyzing the characteristic parameter of the (protein) solution after the experiment. A column may for instance be configured in the flow channel system(s) or chamber(s) by providing a restriction in a flow channel blocking a particle while not blocking a fluid flow, wherein the restriction for instance may be configured by means of an adjustable valve

as described herein configured to trap a particle and not to block the complete fluid flow if the particle is trapped. Especially, by inducing a flow of fluid comprising more than one particle in the channel system(s) and through the restriction, the particles may be blocked by the restriction and may provide a column on top of the restriction. Advantageously, after or during performing a process comprising the particles, the particles may be flushed or circulated by reversing the fluid flow. Especially, by providing a reversed fluid flow with high velocity, the particles may be dragged along with the fluid flow and the column (of particles) may be disassembled. Further, the restriction may also be removed (e.g. by providing the adjustable valve in the first position) when the desired amount of particles are introduced in the flow channel system(s) and the particles may be circulated in flow channel system(s) during performing the process (such as to conduct accurate batch equilibrium adsorption experiments). In another embodiment, a (column of) particle(s) provided on top of the adjustable valve in the second position (configured as a restriction), is/are released, especially when the desired amount of particles is blocked, and especially directed to a further fluid flow channel (of the flow channel system) by providing the adjustable valve in the first position.

In yet another embodiment, the processing device comprises a plurality of (substantially identical) flow channel systems comprising a pump (e.g. comprising a set of further valves) an adsorption isotherm of a protein is determined by (i) providing a fluid flow comprising chromatography particles to the first fluid flow channel; (ii) (sequentially) loading each flow channel system with a specific number of particles by controlling the fluidic device and directing the fluid flow from the second fluid flow channel (sequentially) to each of the flow channel systems (by controlling the channel valves concerned) and determining the total loaded particle surface (in each flow channel systems) from the size of the particles and the number of particles counted during loading; (iii) providing a specific amount of a protein solution to each of the flow channel systems while retaining the particles in the chamber comprised by the flow channel system, wherein the concentration of the protein in the protein solution provided to each flow channel system is known and configured to be different in each flow channel system; (iv) circulating the protein solution comprising the particles by the pump for a sufficient period of time allowing protein to adsorb at the surface of the particles and to establish an equilibrium between the adsorbed amount of protein and

the amount of protein in solution (in each of the flow channels); (v) calculating the amount of adsorbed protein (per m^2 particle surface) from the protein concentration in each of the flow channel systems after the sufficient period of time to obtain an equilibrium and determine the adsorption isotherm of the protein.

In yet another embodiment, the processing device comprises at least one flow channel system comprising a first chamber and at least two flow channel systems comprising a second chamber, wherein especially all chambers are substantially identical chambers comprising a pump (e.g. comprising a set of further valves) for circulating a fluid in the chamber, an adsorption isotherm of a protein is determined by (i) providing a fluid comprising the protein to each of the first chambers, wherein providing a different known initial protein concentrations in different first chambers, (ii) providing the fluid comprising the protein to the second chambers, wherein providing a different known initial protein concentrations in different second chambers, (iii) loading all second chambers with an equal number of particles, comprising a known particle surface area, by a fluidic device (iv), circulating the fluid in the chamber for a specific period of time (allowing the protein to adsorb at the surface of the particles in the second chambers to establish an equilibrium between the adsorbed amount of protein and the amount of protein in solution (in each of the second chambers), (v) determining the protein concentration in solution in the (first and second) chambers, providing the end protein concentration (in solution) in each chamber, (vi) calculating the amount of adsorbed protein (per m^2 particle surface) in each of the second chambers based on the initial protein concentration in a chamber and the end protein concentration in that chamber, (vii) determining the absorbed amount of protein as a function of the initial protein concentration based on the calculated amount of absorbed protein and the initial protein concentration in each of the second chamber providing an adsorption isotherm.

Yet in another embodiment, the processing device comprises at least three pairs of (substantially equal) fluid flow channels, each comprising a first fluid flow channel in fluid contact with a fluidic device, and a second fluid flow channel. In a further embodiment, the processing device comprises at least one pair of flow channel systems, wherein each pair of flow channel systems comprises a first flow channel system comprising a first chamber and a second flow channel system comprising a second chamber, wherein the first chamber and the second chamber comprise substantially the

same dimensions and substantially the same physical parameters, and wherein each first flow channel system is in fluid contact with a fluidic device configured to load a particle in the first flow channel system. Especially, such an embodiment may be advantageously used for determining an effect of a particle on a process wherein the particle is used, by analyzing a parameter of the process in (each of) the first chamber(s) (or first channel system(s)) and comparing the parameter with the value obtained from analyzing the parameter in (each of) the second chamber(s) (or second channel system(s)) comprised in the pair of flow channel systems Hence, especially the second chamber (or second channel system) may provide a reference value of the parameter for the first chamber (or first channel system) of the pair of channel systems. Such an embodiment may be efficiently applied, especially by loading a determined number of particles in each of the first chambers. Herein, "determined" may indicate "predetermined", in the sense that the number of particles introduced to the chamber is known. This term may however also refer to a post determination, in the sense that an unknown or approximately known number of particles are introduced, and after introduction the (precise) number of particles is determined.

In yet a further aspect, the invention also provides a method of controlling a flow of a particle in a fluidic device as described herein, the method comprising flowing a fluid comprising the particle through a fluid flow channel, trapping the particle at the intersection, and flowing a fluid comprising said particle through the other fluid flow channel.

Hence, in an aspect the invention also provides a method for performing a batch adsorption experiment, especially for determining an adsorption characteristic of a molecule to a particle, the method comprising:

- providing the processing device with a plurality of flow channel systems as defined herein;

- loading a determined number of particles in the plurality of flow channel systems providing particle loaded flow channels systems, especially wherein the number of particles in each loaded flow channel system is selected equal, and wherein especially the fluidic device is applied to control loading of the particles in the flow channel systems;

- loading molecules in the plurality of flow channel systems with different concentrations of the molecule in the flow channel systems; and

- determining the adsorption characteristic on the basis of the content of non-adsorbed molecules in the respective flow channel systems and/or on the basis of adsorbed molecules in the respective flow channel systems. In a further embodiment, the molecule is a protein, the particle especially comprises a resin particle having a diameter selected from the range of 0.1–50 μm, and the adsorption characteristic is an adsorption isotherm. Advantageously, the method may comprise circulating the particles in the flow channel systems which may support exposing the surface of the particles to the molecules, and especially may improve reproducibility. Alternatively or additionally, the method may also comprise providing a (packed) column of the particles.

In a specific embodiment, the invention provides a new concept to conduct accurate batch equilibrium adsorption with minimized consumption of materials. An important aspect also is the accuracy in a variety of liquid phase conditions that can be tested. The invention also provides substantial improvement in the accuracy of batch adsorption measurements, by exact metering of the particles applied in the method. In state of the art methods for batch adsorption, frequently multiples of 1,000,000 resin particles are needed, and consumption of reagents per experiment is at least several milliliters, whereas in the processing device described herein 5000 or even less particles may be used, such as in the range of 1000–5000, or 100-1000, or even 1-100 particles, and wherein the amount of reagents may comprise as much as several microliters or even less. Hence, in a specific embodiment, the invention provides the processing device for performing batch adsorption experiments. Especially, the processing device as described herein comprises a closed environment (channel system). Compared to open devices, wherein the liquid may be in contact with a gas atmosphere, a possible evaporation of the liquid phase is reduced and a closed environment may enable working more accurately with smaller liquid volumes over equilibration times. Especially by loading a known number of particles having a specific surface area in the channel system (using the fluidic device as described herein), the total surface area of the particles for performing adsorption experiments is known. It may especially be advantageous that the total surface area of the particles in the channel system and/or the chamber may be calculated from the (known) number of particles and the (known) size of the particles. In contrast to that, in many state of the art devices for batch absorption (experiments), the total surface area of the particles

may be determined from the volume of packed particles, and hence the accuracy of the determined surface area may be affected by random packing effects.

A microfluidic mini-batch reactor has the capability of performing batch adsorption with a nano-scale sample volume for obtaining adsorption isotherms. The automated system includes a unit for capturing defined number of resin particles and a micro-sized peristaltic pump to mix resins and target protein solution. The processes of a batch adsorption experiment on a chip may comprise the sequence of capturing resin particles, pushing the particles into a reactor, loading protein solution into the reactor, circulating particles in protein solution, and determining the concentration of protein solution. The amount of proteins bound on the particles can be calculated from the initial concentration of protein solution and the change of the concentration of protein solution after circulation of particles in the solution. When the sets of the experiments are performed with various concentrations of protein solution, an adsorption isotherm of the target protein is obtained.

Hence, in an embodiment, the invention provides a microfluidic device and method for performing batch adsorption with a factor of 1000 or even 10,000 less (resin) particles, at least a factor of 1000 or 10,000 less volume of reagents, and a factor of 1000 or 10,000 less in the amount of consumed protein compared to state of the art methods for batch adsorption. Aspects of the present application include a capturing module to introduce an exact number of (resin) particles of a pre-defined size into an incubation module or chamber, an incubation module wherein a fluid is circulated while the resin particles are kept the incubation module or wherein the fluid is circulated together with the (resin) particles in the flow channel system, as well as procedures to meter an exact number of particles, keep them in the flow channel system for a specified period of time, flush the particles with fluids of defined composition if required, and release the particles in order to replace them with a new selection of particles.

In another embodiment, the invention provides a processing device for pH-gradient chromatofocusing comprising a micro pH-gradient generator, wherein the pH-gradient generator provides a pH-gradient over the column comprising resin particles loaded in the channel system. When using the processing device for chromatofocusing, fractions (particles) from the column – that may have adsorbed different proteins (because of the different pH values) – may be collected in separate chambers for further

analysis. The required sample consumptions may be very low with 70 nano-liters in the processing device, and all processes may be accomplished automatically. The processing device described herein has the capability of performing batch adsorption with a nano-scale sample volume for obtaining adsorption isotherms. The automated system includes a unit for capturing defined number of resin particles and a micro-sized peristaltic pump to mix resins and target protein solution.

In a further aspect, the invention provides a method to determine an absorption isotherm, the method comprising:

(i) providing the processing device as described herein, comprising at least one flow channel system comprising a first chamber and at least two flow channel systems comprising a second chamber, wherein all chambers are substantially identical chambers comprising a pump (e.g. comprising a set of further valves) for circulating a fluid in the chamber,

(ii) providing a fluid comprising the protein to each of the first chambers, wherein providing a different known initial protein concentrations in different first chambers,

(iii) providing the fluid comprising the protein to the second chambers, wherein providing a different known initial protein concentrations in different second chambers,

(iv) loading all second chambers with an equal number of particles, comprising a known particle surface area, by a fluidic device and circulating the fluid in the chamber for a specific period of time(allowing the protein to adsorb at the surface of the particles in the second chambers to establish an equilibrium between the adsorbed amount of protein and the amount of protein in solution (in each of the second chambers),

(v) determining the protein concentration in solution in the (first and second) chambers, providing the end protein concentration (in solution) in each chamber,

(vi) calculating the amount of adsorbed protein (per m^2 particle surface) in each of the second chambers based on the initial protein concentration in a chamber and the end protein concentration in that chamber,

(vii) determining the absorbed amount of protein as a function of the initial protein concentration based on the calculated amount of absorbed protein and the initial protein concentration in each of the second chamber providing an adsorption isotherm.

Especially, in an embodiment, the invention provides also a method to provide the micro fluidic device. In an embodiment, the device was designed with drawing

software and printed on a soda lime or quartz glass. The valve was fabricated by multilayer soft lithography. Photoresist was spun onto a silicon wafer, and patterned by exposing UV light onto the silicon wafer through the mask. The patterned structures on the silicon wafer were stamped out with PDMS, and holes for inlets and outlets were punched. Two layers of PDMS, one for a fluid layer and the other for a control layer, were aligned and bonded onto a glass slide. In an embodiment, the valve comprises a monolithic valve, especially fabricated in one piece, especially comprising only one material. Especially, the invention comprises a microfluidic device comprising a monolithic valve. Likewise, the invention especially comprises a method to provide the micro fluidic device comprising a monolithic valve.

In yet further embodiments, the (micro) fluidic device may be used in a process to separate particles from a fluid, especially a liquid. In yet a further embodiment, the (micro) fluidic device may be used in process to separate particles from a liquid comprising two or more phases (multi-phase liquid), which are substantially immiscible, wherein the particles are predominantly, such as at least 90% of the particles, available in one of the phases, and substantially not available, such as less than 10% of the particles, in one (or more) other phase(s). Examples of such substantially immiscible liquids may e.g. be a water-in-oil or oil-in-water dispersion, as known to the person skilled in the art. The particles may be gathered in the particle trap. Thereafter, the particles may be released from the trap with a fluid, especially a liquid. This liquid may be another liquid than the liquid wherein the particles were available. In the embodiments wherein the particles were predominantly present in a phase of a multi-phase liquid, e.g. the same liquid as the liquid wherein the particles were available may be used. Also a comparable liquid may be used, such as comparable in terms of polarity, solvability, etc.. In these embodiments, the device as described herein with the first flow channel and the second flow channel may be applied. However, optionally also the other device with the first flow channel may be applied, such as (thus) especially a fluidic device having a particle trap functionality for a particle in a fluid, the fluidic device comprising a first fluid flow channel and a control channel, wherein the control channel at a location is arranged adjacent to the first fluid flow channel and separated by a flexible membrane from the first fluid flow channel, wherein the flexible membrane is configured as a valve, configured in operation at a first pressure in the control channel in a first position not to block

propagation of a particle of a predetermined size in the first fluid flow channel, and at a second pressure in the control channel in a second position to block with said flexible membrane propagation of said particle through the first fluid flow channel, while in this second position not fully blocking fluid flow through the first fluid flow channel. In such embodiments, the valve has an upstream side and a downstream side. The valve is thus at least partly configured in the first fluid flow channel, for blocking or not blocking a particle in the first fluid flow channel. Optionally, at a downstream side, the first fluid flow channel may be branched, to provide two or more channel branches, such as a Y-configuration.

The term "substantially" herein, such as in "substantially consists", will be understood by the person skilled in the art. The term "substantially" may also include embodiments with "entirely", "completely", "all", etc. Hence, in embodiments the adjective substantially may also be removed. Where applicable, the term "substantially" may also relate to 90% or higher, such as 95% or higher, especially 99% or higher, even more especially 99.5% or higher, including 100%. The term "comprise" includes also embodiments wherein the term "comprises" means "consists of'. The term "and/or" especially relates to one or more of the items mentioned before and after "and/or". For instance, a phrase "item 1 and/or item 2" and similar phrases may relate to one or more of item 1 and item 2. The term "comprising" may in an embodiment refer to "consisting of" but may in another embodiment also refer to "containing at least the defined species and optionally one or more other species".

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

The devices herein are amongst others described during operation. As will be clear to the person skilled in the art, the invention is not limited to methods of operation or devices in operation. It should be noted that the above-mentioned embodiments illustrate rather than limit the invention, and that those skilled in the art will be able to design many alternative embodiments without departing from the scope of the

appended claims. In the claims, any reference signs placed between parentheses shall not be construed as limiting the claim.

Use of the verb "to comprise" and its conjugations does not exclude the presence of elements or steps other than those stated in a claim. The article "a" or "an" preceding an element does not exclude the presence of a plurality of such elements.

The invention may be implemented by means of hardware comprising several distinct elements, and by means of a suitably programmed computer. In the device claim enumerating several means, several of these means may be embodied by one and the same item of hardware. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage.

The invention further applies to a device comprising one or more of the characterizing features described in the description and/or shown in the attached drawings.

The invention further pertains to a method or process comprising one or more of the characterizing features described in the description and/or shown in the attached drawings.

The various aspects discussed in this patent can be combined in order to provide additional advantages. Furthermore, some of the features can form the basis for one or more divisional applications.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the invention will now be described, by way of example only, with reference to the accompanying schematic drawings in which corresponding reference symbols indicate corresponding parts, and in which:

Fig. 1 schematically depicts a standard on/off valve;

Fig. 2 schematically depicts an adjustable valve as described herein;

Fig. 3 schematically depicts the (micro) fluidic device;

Fig. 4 schematically depicts an embodiment of the process device as described herein;

Fig. 5 schematically depicts an aspect of an embodiment of the processing device comprising a plurality of flow channel systems;

Figs. 6a, 6b, and 6c schematically depict aspects of an embodiment of a processing device comprising a plurality of flow channel systems;

Figs 7a-7b schematically depict aspects of an embodiment of a processing device;

Fig 8 schematically depicts an aspect of an embodiment wherein the v-valve is used for flexible particle packing and releasing in a microfluidic channel; and

Fig. 9 schematically depicts an aspect of an embodiment wherein the v-valve is used for particle sieving and releasing.

Corresponding reference symbols used in the description and in the figures indicate the same or corresponding parts. The drawings are not necessarily on scale.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Figures 1a-1d schematically depict a microfluidic valve 3 known in the art. The valve 3 provided in a flow channel 10, is a binary valve 32 also indicated herein as an on/off valve 32, a shut-off valve 32 and a push-up shut-off valves 32. The valve system especially may consist of two layers providing two channels, a top fluidic layer defining a first fluid flow channel 10 and a bottom control layer comprising a membrane 17 and a control channel 13. Applying pressure to the control channel 13 actuates the membrane 17 between the two layers and the membrane blocks the cross sectional area of the fluid flow channel 10 wherein the valve 32 is located. Because the displacement of the membrane 17 increases with the increase of the applied pressure, the fluid flow channel 10 is completely blocked when the applied pressure is higher than a certain threshold pressure. Hence especially the on/off valve 32 comprises two settings or conditions: the first condition is a closed setting blocking the flow channel 10 completely and the second condition being an “open” setting allowing a flow to pass the valve 32. Hence, in the closed setting (fig. 1c) the effective passageway area 35 is substantially zero (and therefore not shown in the figure), while in the open setting (fig. 1a) the effective passageway area 35 is substantially equal to the cross sectional area 19 of the flow channel 10 (wherein the cross sectional area 19 of the fluid flow channel 10 is the area of an intersection of the fluid flow channel 10 with a plane perpendicular to a channel axis 18 of the fluid flow channel 10). Especially, since the channel height and the channel width of flow channel 10 may not necessarily be equal, herein the equivalent circular diameter of the flow channel 10 may be defined as two times the

square root of [the cross sectional area 19 of the fluid flow channel 10 (not blocked by a valve 3) divided by π].

In the fig. 1a, a fluid flow channel 10 and a control channel 13 are shown, wherein a membrane 17 separates the fluid flow channel 10 from the control channel 13. Schematically this is also depicted as a top view in Fig. 1b where the fluid flow channel 10 is "on top" of the membrane 17. To close the valve 32 the pressure in the control channel 13 is increased so that the flexible membrane 17 is "lifted" and completely fills and blocks the fluid flow channel 10, as is schematically depicted in Fig. 1c (and 1d). In Fig. 1d, the membrane fills the fluid flow channel completely at the location where the control channel 17 intersects the fluid flow channel 10.

Figures 2a-2d depict the adjustable valve 31 according to the present invention wherein the valve 31 is in the second position/the membrane 17 is in the second position because of the second pressure in the control channel 13. (In a first position of the membrane, the schematic picture of the adjustable valve 31 would look exactly the same as for an on/off valve 32 as is depicted in the figures 1a and 1b.) Fig. 2d schematically depicts a top view comparable to the figures 1b and 1d of the valve 3, and Fig. 2a-2c depict cross-sectional views of the adjustable valve respectively represented at the locations A—A, B—B and C—C indicated in Fig. 2d. The (adjustable) valve 31 in the second position is configured to trap a particle of a predetermined minimum size while it never completely blocks the fluid flow channel 10 (the fluid flow, however, may be blocked by a particle trapped in the valve) and is configured in a flow channel wherein a flow especially flows in the direction from A to C. The adjustable valve 31 has a funnel-type shape or v-type shape, and especially comprises a tapered or conical shape, as can be seen in especially Fig. 2d (and hence also the name v-valve or v-type valve may be used herein to refer to an adjustable valve 31) and from the successive Figs 2a, 2b, and 2 c. Especially, the valve 31 is configured to provide in a gradual increasing blockade of a cross sectional area 19 of the first fluid flow channel 11, especially a gradual decrease of the effective passageway area 35, in a direction parallel to a longitudinal axis of the first fluid flow channel 11. Because of this shape i.e. a shape wherein in the second position of the membrane 17, the (adjustable) valve 31 does not block the cross sectional area of the fluid flow channel 10 at the upstream side of the valve (see fig. 2a), whereas the blockade of cross sectional area of the fluid flow channel increases, and thus the effective passageway

area 35 gradually decreases, in the direction towards the downstream side of the valve as can been seen from figures 2a-2c. Optionally, the effective passageway area 35 may increase again at the side of the valve opposite to the upstream side of the valve (not in the depicted embodiment; however in embodiment of the v-shaped valve comprising an hour glass shaped valve this situation may appear). By changing the controllable pressure in the control channel 13, the effective passageway area 35 at a given location may further be controlled in a continuous way and therewith controlling the size of particles that are not able to pass the adjustable valve 31. Fig. 2a-2c also show that the control channel 13 is, at a location, arranged adjacent to the first fluid flow channel 10 and separated by a flexible membrane 17 from the first fluid flow channel 10.

In fig 2e, the geometry of a v-type valve 31 is depicted, wherein the valve, having a valve width w (equal to the width of the (first) fluid flow channel 10 at the intersection) and a length l, comprises a first valve section 41 having a length l_1 and a second valve section 42 having a length l_2. The first valve section is configured to comprise the upstream side 38 of the valve, whereas the second valve section includes the downstream side 39 of the valve. One of the walls of the valve 31 comprises the membrane 17 adjacent to the control channel (see figs 2a-2c). Especially, only in the second valve section 42, the membrane 17 comprises substantially the complete width w of the v-type valve 31, whereas in the first valve section 41, only a fraction of the valve width w is comprised by the membrane 17. The second valve section length l_2 may be larger than the first valve length l_1, such as two or four times as large. However, the second section length l_2, especially, is substantially equal to or smaller than the first section length l_1. The ratio l_2/w may for instance be in the range of 0.05–1, such as 0.1–0.6, depending, for instance on the flexibility of the membrane 17 and the applied pressure. Especially, if the second valve part length l_2 is very long, the valve 31 may completely block the fluid flow in the (first) flow channel 10 in the second valve section 42, whereas it may also be possible that the second section length l_2 is too small to provide the blockage of the first fluid flow channel 10 required to block a particle.

In figures 3a-3c, the fluidic device 1 having a particle trap functionality for a particle 2 in a fluid is schematically depicted. The fluidic device 1 comprises a first fluid flow channel 11, a second fluid flow channel 12, and a control channel 13 (not shown in Figs. 3a-3c). The first fluid flow channel 11 is in fluid contact with the second fluid flow channel 12 at the intersection 14 where also an adjustable valve 31 is

arranged. Depending on the pressure in the control channel, the adjustable valve 31, may block propagation of a particle 2 of a predetermined size flowing in the first fluid flow channel 11 see figs 3a and 3b, or (in the first position of the membrane 17), it may not block any particle 2.

In figs 3a-3c also two first channel valves 36 and two second channel valves 37 are depicted respectively in the first fluid flow channel 11 and the second fluid flow channel 12. The two first channel valves 36 are each provided at opposite sides of the intersection 14 and may be used to completely block the first fluid flow channel 11 at both sides of the intersection 14. The same holds for the two second channel valves 37 and the respective second fluid flow channel 12. During operation this way a fluid flow in the first and second fluid flow channels 11, 12 can be controlled by controlling the first and second channel valves 36, 37. In this embodiment the channel valves 36, 37 are configured as on/off valves 32, however, a channel valve may also be configured as a one-way valve or check valve. In the figures 3, but also in other figures, a closed on/off valve 32 is indicated by means of hatching. Likewise, an adjustable vale 31 in the second position is indicated by means of hatching.

A way to catch a particle 2 from a flow in the first fluid flow channel 11 and successively introduce the particle in the second fluid flow channel 12 is depicted in figs 3a to 3c: a particle 2 may be caught from the flow in the first fluid flow channel 11 by the adjustable valve 31, by allowing (by opening the first channel valves 36) a fluid containing a particle 2 to flow in the first fluid flow channel 11 and setting the adjustable valve 31 in the second position of the valve; at the same time the flow in the second fluid flow channel is blocked by the two second channel valves 37 (see fig 3a). Once a particle 2 having a larger diameter than the minimum effective passageway (see 35 in figs 2a-2c) enters the adjustable valve 31, the particle will be caught, see fig 3b. Next, the fluid flow in the first fluid flow channel may be blocked by closing the two first channel valves 36; and once a fluid flow is started in the second fluid flow channel 12 (by opening the second channel valves 37), the particle 2 will be introduced in the fluid flowing in the second fluid flow channel once the particle is released (by setting the adjustable valve 31 in the first position) from the adjustable valve 31.

In Fig. 4, a processing device 100 comprising the fluidic device 1 is schematically depicted. The processing device further is equipped with an introduction system 110 to introduce a fluid flow with one or more particles 2 into the first fluid

flow channel 11 of the fluidic device 1. Different introduction systems such as all kinds of pumps known in the art may be applied. The introduction system 110 may for instance comprise a rotary pump, a syringe pump, a peristaltic pump, or even a pumping system with a pressure regulator. The device 100 further comprises a flow channel system 120 (coupled to the second fluid flow channel 12) with a chamber 125 to performing a process using one or more particles 2. To monitor the process, the device also comprises an analysis system 126. Optionally the device comprises a detection system 130 to detect a caught (trapped) particle 2 at the intersection 14. If a particle is detected the valves 31, 36, 37 in de fluidic device 1, e.g., may be controlled via a connecting wire 145 by the control system 140 to load the detected particle 2 in the flow channel system 120. In an embodiment the control system 140 may also be configured to control the introduction system 110 via a connecting wire 145. In Fig. 4, the control channel is not depicted, but may especially be configured below the plane of drawing, and is especially adjacent at location 14.

In the schematically depicted embodiment, the particle 2 is directed into the chamber 125 provided with a column support 181. Hence a column 180, such as a chromatography column, may be arranged from the particles 2 that are loaded into the chamber 125. For separation and/or other purposes, the second flow channel 12 may not necessarily be available. For instance, one may capture particles with the valve 31, with the flow flowing e.g. in a first direction downstream of the valve 31, such as e.g. in a straight flow from 110 to the entire right part of the drawing. After having captured the desired particle(s), the particles maybe release and the flow may e.g. be steered to the first and/or second right fluid flow channels 10.

In Fig. 5, a part of processing device 100 comprising a plurality of flow channel systems 120 in fluid contact with the second fluid flow channel 12 is schematically depicted. Each of the flow channel systems 120, may be loaded (sequentially) with one or more particles caught by the fluidic device 1 by directing the flow in the second fluid flow channel to the specific flow channel 120. For this, the processing device further comprises a second fluid flow direction system 45 configured to control the fluid flow in the second fluid flow channel 12 to each of the plurality of flow channel systems 120. Especially, in the embodiment depicted in Fig. 5, the second fluid flow direction system 45 comprises valves 32 in the fluid flow channels connecting the second fluid flow channel to the each of the flow channel systems 120. The second fluid flow

direction system 45 may for instance be controlled by the control system 140. In the specific embodiment depicted in Fig. 5 the processing device 100 only comprises one analysis system 126. However, in other embodiments the device 100 may comprise more than one analysis system 126. In Fig. 5, the control channel is not depicted, but may especially be configured below the plane of drawing, and is especially adjacent at location 14.

In Fig. 6, schematically a multichannel system microfluidic device 200 is depicted. The multichannel system microfluidic device 200 may in embodiments comprise at least one fluidic device 1 and hence provide an embodiment of the processing device 100 according to the present invention, whereas in other embodiments the multichannel system microfluidic device 200 may not comprise a fluidic device. The aspects of the multichannel system microfluidic device 200 will first be discussed more in general referring to Fig. 6a. In Fig. 6a some aspects of an embodiment comprising a plurality of flow channel systems 120 comprising a chamber 125 is depicted. Such an embodiment may especially be explained for determining an adsorption isotherm of a protein on a particle 2. In an adsorption isotherm the amount of adsorbed solute on the surface of a particle is determined as a function of the initial concentration of the solute in the solution. Thus, for determining the adsorption isotherm of a protein (on a particle) the amount of adsorbed protein on the surface of a particle has to be determined as a function of the initial concentration of protein in the protein solution (around the particle). When a protein solution is provided in a chamber 125 comprising particles 2, the protein, however may also be adsorbed at other surfaces, such as a surface of a wall of the chamber 125. Hence, especially for determining an adsorption isotherm in a chamber 125, it may be relevant to determine the adsorption of the protein on the chamber 125 comprising particles 2 and to determine the adsorption in the same chamber 125 or in an equivalent chamber 125 not comprising particles 2.

In the embodiment depicted in Fig. 6a the multichannel system microfluidic device 200 comprises pairs of chambers 125, all pairs comprising a first chamber 125' (depicted at the left hand side of the figure) and a substantially equal second chamber 125'' (depicted at the right hand side of the figure). Especially, in the Fig. nine pairs of substantially equal chambers 125' and 125'' are depicted. In Fig. 6b a part of Fig. 6 is exploded showing only one second chamber 125'' (comparable to the first chamber

125'comprised in the pair of chambers and not depicted in detail), that may be divided in a particle (introduction) zone 120a, a dilution (introduction) zone 120b and a protein (introduction) zone 120c. For all nine second chambers 125'' and all nine first chambers 125', the volume of the particle zones 120a is equal, and the volume of the dilution zone 120b plus the volume of the protein zone 120c is equal, however, the ratio between the volume of the dilution zone 120b and the volume of the protein zone 120c changes of between the nine different second chambers 125''. The nine first chambers 125' are configured the same as the nine second chambers 125''. Although this configuration with depicted dimensions of the chambers and zones may be convenient for determining an adsorption isotherm, this is not essential. Hence, in other embodiments the dimensions of the different zones 120a, 120b, and 120c for the different first and second chambers 125'and 125'' may be differently selected.

When an experiment is started, the protein solution with a known protein concentration is provided to the protein zone 120c of all first 125' and second chambers 125''. By supplying the protein solution to the protein input channel 140, setting the valves 32 concerned by opening the respective control port 135 for the on/off valves, the protein solution will first flow through all protein zones 120c of all second chambers 125', and successively also will fill the protein zones of all first chambers, 125''. All chambers are filled when the flow may leave the system again via the protein outlet 141. The dilution zones 120b of all chambers 125', 125'' may be filled by the same principle with a dilution solution provided at the buffer solution input 142. The particle zones 120a of the first chambers 125' may not be loaded with a particle, these zones 120a of all first chambers 125' may be provided with a second buffer solution provided at the second buffer solution 142. Successively, the nine second chambers 125'' may simultaneously or sequentially be loaded with a known number of particles 2 (the number of particles especially being the same for all second chambers 125'', however the number of particles may also differ), by providing a flow comprising particles in the first fluid channel 11, capturing particles upstream of the second chambers 125'' and introducing the particles 2 into the chambers 125'' by providing a fluid flowing through the second fluid flow channel 12. If the desired number of particles are loaded in the nine second chambers 125'', the valves are controlled in such a way that no fluid can leave the chambers 125', 125'', and the fluid may be circulated in the flow chambers by controlling the three valves 32 configured as a pump 33. In

some embodiments of the multichannel system microfluidic device 200, the particles may also freely flow through the chambers 125, being dragged along by the fluid flow. In other embodiments, like the one schematically depicted in Figures 6a and 6b, a restriction or filter element 150 is arranged in the flow channel of the chambers 125', 125''. This restriction or filter element 150 may comprise a filter 151 to avoid particles 2 to pass. Especially, when the device comprises this restriction a circulating flow may refer to a back and forth flow in the chamber 125''. The fluid flow may repeatedly drag the particles in the direction of one side of the restriction during a first period, and in the direction of the other side of the restriction during a second period. Such embodiment may for instance be beneficial for a process with a particle wherein the progress of the process may be followed by observing a change in a fluid characteristic (of especially a fluid without particles). For instance such an embodiment may advantageously be applied for determining an adsorption isotherm of a protein using proteins with a fluorescence label, wherein the color of the fluid may indicate the protein concentration of the fluid and wherein the concentration of the protein solution may be measured by in-line determining the color of the fluid without the particles in or through the flow channel of the chamber 125''. Such restriction or filter element 150 may also advantageously be used to prevent a particles to exit the chamber 125'' if a sample of the fluid is removed from the chamber e.g. for an analysis elsewhere in an analysis system integrated with the processing device, or optionally configured external of processing device. The experiment may be stopped when the concentration of protein in the fluid is in equilibrium with the amount of protein adsorbed at the particle surface. The concentration of protein adsorbed in each second chamber 125'' may be calculated from the known protein concentration, the ratio between the volume of the dilution zone 120b and the volume of the protein zone 120c, and the amount of protein absorbed in the respective first chamber 125'. The amount of protein absorbed per m^2 of particle surface in each of the second chamber 125'', successively may be calculated from the amount of protein absorbed in the respective second chamber 125'' and the total surface area of the particles in that respective chamber 125'' as calculated from the number of particles 2 and the surface area per particle 2. Especially, the embodiment is configured with pairs of equal chambers 125' and 125'' that are provided with the same amount of protein at the start of the experiment, enabling to correct for absorption of protein on the (walls of the) chamber. This configuration may

also enable the use for instance of labeled proteins with a fluorescence label that may show a degradation in time, while still being able to determine the concentration of the protein in solution (in the second chamber 125'' by comparing the results obtained in the first chamber 125').The multichannel system microfluidic device 200 schematically depicted in Fig. 6a may advantageously comprise at least one fluidic device 1 according to the present invention for loading a controlled number of particles in the second chambers 125'' and hence comprise the processing device 100. Especially in such an embodiment, the fluidic device 1 may be configured upstream of the second fluid flow direction system 45. Fig. 6c for instance schematically depicts an embodiment comprising the combination of a fluidic device 1 and a second fluid flow direction system 45 that may be configured at the location schematically depicted by the area indicated with 6c in Fig. 6a and thus resulting in an embodiment of the processing device 100 according to the present invention.

In Fig. 7a schematically (a photolithographic mask design (Clewin software)) of an aspect of an embodiment of a processing device 100 is given. Based on that design, a processing device 100 comprising an adjustable valve 31 and a plurality of on/off valves 32 is provided, see Fig. 7b wherein enlarged views (see the box indicated in Fig. 7a) of the processing device 100 at different stages are depicted. The device 100, may be used to catch particles 2 form a first fluid flow channel 11 and to successively introduce the trapped particle(s) 2 in a second fluid flow channel 12. A particle may be caught by configuring the adjustable vale 31 in the second position and providing a fluid flow comprising a particle 2 in the first fluid flow channel 11. Next, the valves 32 may be set in such a way that the flow in the first fluid flow channel 11 is blocked and a flow in the second fluid flow channel 12 is not blocked. Using that valve setting, while setting the adjustable valve 31 in the first position, may free the caught particle 2 again, after which the particle 2 is dragged along with the fluid flow in the second fluid flow channel 12. Again hatched on/off valves 32 represent closed valves and a hatched adjustable valve 31 represents the second position of the adjustable valve. Arrows indicate the direction of flow in a fluid flow channel 11, 12. In Fig. 7b the process of catching a particle 2 and introducing the particle 2 is schematically elucidated by depicting the status of the processing device 100 at twelve successive moments in time, indicated by the successive roman numbers I – XII. For clarity reasons not all reference numbers are indicated in all of the twelve statuses of device

100. The processing device 100 in Fig. 7b comprises five chambers 125 arranged in series in the second fluid flow channel 12. Depending on the setting of the on/off valves 32 in the second fluid flow channel 12 sequentially arranged chambers 125 may either be in open connection with each other or be isolated from each other by setting the on/off valve 32 arranged in the second fluid flow channel 12 between the respective reactor respectively in the "open" or "closed" mode. As is schematically depicted by the statuses I – III, the processing device 100 may be used to catch (or sieve) a (number of) particle(s) 2 from the first fluid flow 11 (status II) and successively the trapped particle 2 may be introduced into the chamber 125 that is arranged first in line downstream of the adjustable valve 31 (in the second fluid flow channel 12) (status III). If that chamber 125 already comprises (a fluid comprising) a particle, the content in that chamber 125 may also be transferred to the adjacent chamber 125 by setting the on/off valves 32 separating the two chambers 125 in concern is in the "open" setting, see e.g. statuses III - V. Based on the same approach, the content (the fluid comprising a particle 2) in the second chamber 125 may be transferred to the third chamber, etc., etc., as is schematically depicted in the figure. Hence, using the process all five chambers 125 may be provided with a particle 2 sieved from the first fluid flow channel 11. It may be understood that by selecting the number of particles to be caught by the microfluidic device 1 at a specific moment, also the number of particles 2 in a specific chamber 125 may be controlled.

The introduction of the particle 2 may be provided by any kind of fluid provided to the second fluid flow channel 12. The fluid may be the same kind of fluid that is also flowing in the first fluid flow channel 11. The fluid may also comprise another (type of) fluid. Especially the fluid used to introduce the trapped particle 2 may comprises a gaseous fluid. In the depicted example the fluid in the first fluid flow channel 11 comprises a liquid, and the fluid used to introduce the trapped particle 2 in the second fluid flow channel 12 (at the upstream side of the adjustable valve 31) comprises a gas (and hence is only indicated by an arrow in the figure, whereas as liquid in the channels is indicated by hatches (in Fig. 7b being different from the hatches used for indicating a closed valve 32 and v-valve 31in the second position)). By using a gas such as air, the pressure in the different chambers 125 may especially be kept equal. Especially, small difference in pressure may cause differences in volume between sequential chambers 125.

Fig. 8 schematically depicts an aspect of an embodiment wherein the adjustable valve 31 is used to provide a flexible particle packing or (packed) column 180 comprising particles 2 in a fluid flow channel 10. In this embodiment the adjustable valve 31 in the second position (indicated by hatching) may provide a (dynamic) restriction in the fluid flow channel 10 preventing a particle 2 (of a minimal dimension) to pass. A column 180 may be formed upstream of the restriction. In the Fig. several stages (I, II, III, IV, V) of forming and releasing the column 180 in the fluid flow channel 10 are schematically depicted. The five adjustable valves 31 in Fig. 8 each represent a different moment in time t providing different stages in the forming and releasing process. Herein, stage I may represent the adjustable valve 31 at $t = t_I$, stage II represents the adjustable valve 31 at $t = t_{II} > t_I$, stage III represents the adjustable valve 31 at $t = t_{III} > t_{II}$, stage IV represents the adjustable valve 31 at $t = t_{IV} > t_{III}$, and stage V represents the adjustable valve 31 at $t = t_V > t_{IV}$.

By providing a flow comprising particles 2 in the fluid flow channel 10, the particles 2 may be caught by the adjustable valve 31 after setting the adjustable valve 31 in the second position at $t = 0$, therewith trapping the particles 2 at the upstream side 38 of the adjustable valve 31 at $t = t_I$ in stage I. While continuously providing the flow comprising particles 2 in the fluid flow channel 10, a column 180 comprising the trapped particles 2 is provided as long as the adjustable valve 31 remains in in the second position, see stage II and stage III. Successively e.g. in an embodiment a process wherein the column 180 of particles 2 is used may be performed in the fluid flow channel 10. (In another embodiment the fluid flow channel 10 (comprising the adjustable valve 31) may e.g. be part of a fluid flow channel system and the column may only be used to trap a determined amount of particles 2 before further directing the determined amount of particles (simultaneously) into the fluid flow channel system.) Finally, the column 180 may be released by setting the adjustable valve 31 in the first position, see stage IV and V, allowing propagation of the particles 2 in the fluid flow channel 10 (and optionally further in the fluid flow channel system).

Fig. 9 schematically depicts an aspect of the adjustable valve 31, wherein the adjustable valve 31 is used for particle sieving and releasing. Similar to Fig. 8, in Fig. 9 also five stages (I, II, III, IV, V) are schematically depicted in the same fluid flow channel 10 and a hatched adjustable valve 31 indicates the valve 31 in the second position. Again, stage I represents the adjustable valve 31 at $t = t_I$, stage II represents

the adjustable valve 31 at $t = t_{II} > t_I$, stage III represents the adjustable valve 31 at $t = t_{III} > t_{II}$, stage IV represents the adjustable valve 31 at $t = t_{IV} > t_{III}$, and stage V represents the adjustable valve 31 at $t = t_V > t_{IV}$. In Fig. 9 a flow of a first fluid 310 is provided to the fluid flow channel 10. The first fluid 310 comprises droplets 325 of a second immiscible fluid 320. By providing the second position to the adjustable valve 31 a particle 2 that may be present in a droplet 325 may be caught, whereas the droplet 325 may pass. This process is schematically represented in stage I. At stage I (a droplet 325 comprising) the immiscible fluid 320, transported by the first fluid 310 enters the adjustable valve 31 at the upstream side 38 of the valve 31. Because of the flexibility of the droplet 325, the immiscible fluid 320 passes the valve 31 in the second position, whereas the particle 2 is trapped in the adjustable valve 31, see stage II, and the droplet 325 may exit the adjustable valve 31 again at the down stream side 39 leaving the particle in the adjustable valve 31, see stage III. The process of sieving particles 2 from a second immiscible fluid 320 may be repeated a number of times, ending up with a number of particles 2 trapped in the adjustable valve 31, see stage IV. Successively all particles 2 may be released again from the adjustable valve 31 by setting the adjustable valve 31 in the first position when a droplet 325 of immiscible fluid 320 is passing the adjustable valve 31, see stage V.

Also in Figs. 8-9, like in many other drawings, the control channel is not depicted, but may especially be configured below the plane of drawing. Referring to these figures, in embodiments downstream of the valve 31, the first fluid flow channel (here simply indicated as fluid flow channel 10) may optionally include one or more bifurcations, such as e.g. a Y-shaped bifurcation. For instance, during collection of the particles 2, the fluid may flow in a first direction, and when the collected particle(s) 2 is (are) released from the valve 31, the fluid including the particle(s) may flow in a second direction (not shown in the drawings). Note that in these drawings the fluid flows from right to left. Referring to Fig. 9 I-III, the fluid may be provided in a first direction (not shown), and in Fig. 9 IV-V the fluid may flow to a second direction (see also comments Fig. 4).

It should be noted that the above-mentioned embodiments illustrate rather than limit the invention. Based on the above-mentioned information, those skilled in the art will be able to design many alternative embodiments without departing from the scope of the appended claims.

EXPERIMENTAL

Here, we developed a flexible microfluidic v-type valve system, which can trap particles or cells in a fluid in a micro channel. The v-type valve was designed to generate a focused flow in the center of a channel by the flexible actuation of a PDMS membrane. The position of valve and the degree of blockage of the valve is adjustable therefore the system allows to control over the size of the particles that are blocked by the valve. Furthermore the v-type valve not only allows to catch particles from a liquid stream in a micro channel and to trap particles in the adjustable valve, but also enables the release of the particles into a second micro channel. This second channel could then be connected to a reactor in which a process can be performed in which the particle is involved, e.g. a catalytic process, an adsorption process, or (if the particle is a cell) a biological experiment. We developed and tested various designs of the v-type valve to optimize the actuation of the valves and evaluate the functionality of the valve to capture and release particles and cells in a fluid flow. We also demonstrated the smart uses of a v-type valve in combination with general monolithic PDMS valves for 1) the generation of a solid phase column, 2) the isolation of the desirable number of particles in micro reactors, and 3) the separation of particles from a liquid droplet in two immiscible fluid flows.

Valves with different design parameters were fabricated by multilayer soft lithography and characterized at various operating pressures. To evaluate the functionality of the valve, single micro particles (Ø 7 μm and Ø 15 μm) and single cells (Ø 20 μm) were trapped from flowing suspensions. Continuous processes of particle capture and release were obtained by controlling the actuation and deactuation of the valve. Integration of the v-type valve with poly(dimethyl siloxane) (PDMS) monolithic valves in microfluidic devices was demonstrated to illustrate the potential of the system in various applications such as the creation of a solid phase column, the isolation of a specific number of particles in reactors, and the capture and release of particles or cells in the flow of two immiscible liquids.

Materials and methods

Materials

Source 15Q (Ø 15 μm particles based on rigid polystyrene/divinyl benzene polymer matrix) was purchased from GE Healthcare Life Sciences (GE Healthcare

Europe GmbH, Eindhoven, The Netherlands), and diluted 1:1000 in Milli-Q water for testing particle capture and 1:100 for testing particle packing. CountBright Absolute Counting Beads (Ø 7 μm particles for flow cytometry) were obtained from Molecular Probes (Life Technologies Europe BV, Bleiswijk, The Netherlands). 100 μM of resorufin (Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands) solution was prepared in Milli-Q water to visualize the actuation of valves in micro channels. We used mineral oil (Sigma-Aldrich Chemie BV, Zwijndrecht, The Netherlands) and Source 15Q suspension in Milli-Q water to generate droplets in oil flow.

Cell culture and preparation

The prostate cancer cell line, PC3 (PC-3 (ATCC CRL-1435), was cultured in RPMI-1640 media (Sigma Aldrich, Zwijndrecht, The Netherlands), supplemented with 10% Fetal Bovine Serum (Sigma Aldrich) and 1% Penicillin-Streptomycin (Sigma Aldrich) at 37 °C in 5 % CO_2 atmosphere. Before experimentation, cells were stained with CellTracker Orange CMTMR (Molecular Probes, Breda, The Netherlands) at 37 °C for 30 min and detached them from the culture flask by 0.05 % of Trypsin/EDTA (Gibco, Paisley, UK). Thereafter, cells were washed once with the culture medium and re-suspended in PBS solution at a concentration of 500,000 cells/ml.

Chip fabrication

The microfluidic chips consist of a PDMS fluidic layer and a PDMS control layer; and are fabricated by multilayer soft lithography technique (as described by Xia, and Whitesides (1998) *Annual review of materials science* (1998), 28(1), p. 153-184, and by Unger *et al.* (2000), *Science* 288(5463): p. 113-116). To prevent non-specific binding of fluorescent molecules on PDMS surfaces, fluidic channels are treated with copolymer pluronic 10 g/L (Millipore, Zug, Switzerland) for 5 min and washed with Milli-Q water for 30 min.

Characterization of the device profile

Fabricated devices were sliced by a surgical blade to measure average values of the channel height and membrane thickness. The microscope images of the cross-sectional view of the sliced device were acquired by an inverted microscope (Leica DMI 5000M) and analyzed by Leica imaging software (Leica Application Suite, Leica Microsystems BV, The Netherlands).

Chip operation

The microfluidic devices were controlled by a pneumatic control system. Micro-valves were operated by applying compressed nitrogen gas into control channels. The pneumatic control system was automated by combining precision pressure regulators, 3/2-way solenoid valves, and EasyPort USB digital I/O controller (all from Festo, Festo BV, The Netherlands). We controlled the pneumatic system by a custom-built LabVIEW (National Instruments Co.) program.

Data processing

We used an inverted fluorescent microscope (Leica DMI 5000M, 10X, 20X, and 40X Objectives, Leica Microsystems BV, The Netherlands) equipped with an automatic XY-stage (Oasis PCI XY control unit), and a digital camera (Leica DFC300 FX, Leica Microsystems BV, The Netherlands) for acquisition of images to monitor the actuation of valves. The fluorescent signal from resorufin was observed by a Leica N 2.1 filter cube (excitation: BP 515 - 560 nm; emission: LP 590 nm) and the fluorescent images of Source 15Q and CountBright Absolute Counting Beads were acquired by a Leica I3 filter cube (excitation: BP 450 - 490 nm; emission: LP 515 nm). All the acquired images were processed and analyzed by the image calculator and interactive 3D surface plot of Image J software (http://rsb.info.nih.gov/ij/).

Valve design

For the realization of the functionality of a v-shaped valve, v-type valves with various dimensions have been designed and tested. Table 1 shows the dimensions of 8 different v-valve designs. When the valve area where a membrane forms between fluidic and control layers is increased, the actuation of the membrane at a constant applied pressure is also increased. Hence, 8 different designs of v-valves with various ratios of length of the valve (l_2) and width of the channel (w) have been designed for optimization of the dimensions of v-valves. The ratio of l_2 and w ranged from 0.2 to 0.9. The height of the channel was designed at 35 μm. The characterization showed an average channel height of 37.6 ± 0.4 μm and an average membrane thickness of 14.7 ± 0.5 μm from 15 microscope images of three different devices.

Valve design	Channel width (w) [μm]	Length of the valve sections		l_2/w
		l_1 [μm]	l_2 [μm]	
#1	100	125	20	0.2
#2	100	125	30	0.3
#3	100	125	40	0.4
#4	100	125	50	0.5
#5	100	125	60	0.6
#6	100	125	70	0.7
#7	100	125	80	0.8
#8	100	125	90	0.9

Valve actuation

Optimal dimension of a valve to form a v-type valve

The v-type valves with different dimensions have been tested at various applied pressures ranged from 0 bar to 2.0 bar. For the visualization of the displacement of the valves, 0.1 g/l of Rhodamine B isothiocyanate–Dextran (average MW ~ 10,000, Sigma-Aldrich) solution was introduced into the fluidic channel and the change of the fluorescent intensity according to various applied pressures was monitored by a fluorescent microscope (Leica DM 5000).

At a given pressure and depending on the ratio l_2/w the actuation of the valve starts from the two sides of the fluidic channel, therefore a focused flow was generated at the center of the channel. It was observed that with increasing l_2/w focused flow manifested at decreasing pressure, whereas at a constant pressure the intensity of the actuation at the center of the fluidic channel showed an increase with increasing l_2/w, eventually leading to a substantial complete blockage of the fluid flow channel.

Valve design	l_2/w	Min pressure for focused flow [bar]	Pressure at blockage [bar]
#1	0.2	0.4–0.5	1.3–1.4
#2	0.3	0.3–0.4	0.9
#3	0.4	0.3	0.6–0.7
#4	0.5	0.2	0.5

#5	0.6	0.1–0.2	0.4
#6	0.7	0.1–0.2	0.3–0.4
#7	0.8	0.1	0.3
#8	0.9	0.1	0.2–0.3

Particle capture by a v-type valve

To optimize the operating pressures of v-type valves to capture particles of a desired size, the actuation of valve by various applied pressures (0–2.0 bar) was studied with v-type valve design #1, #2, #3, and #4. At a constant operating pressure, the focused flow is created at the center of the channel where the actuation of a v-valve is the lowest. Hence the size of particles that can be captured by v-type valves depends on the height of the membrane at the center of the channel. The next table shows the height of the valve in μm at the center of the channel for various relevant operating pressures in the range from 0.2 bar to 1.5 bar.

Valve	Applied pressure [bar]												
	0.2	0.4	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2	1.3	1.4	1.5
#1	4.0	6.3	7.3	8.3	10.0	10.3	11.7	13.7	14.7	16.7	18.3	18.3	21.0
#2	6.0	9.3	11.0	12.3	14.0	15.7	16.3	18.7	20.3	21.7	23.7	24.7	26.3
#3	7.7	12.3	14.3	16.0	18.7	20.7	23.0	24.3	26.3	27.7	29.7	30.7	32.0
#4	9.3	15.7	18.7	20.0	22.7	24.7	28.0	29.3	31.3	33.3	34.3	34.3	35.3

We used the V-type valve with valve design #4 to capture a Ø 15 μm particle, a Ø 7 μm particle, and a single PC3. We pushed particle suspensions with 0.1 bar into a fluidic channel while the valve was actuated by applying 0.7 bar and 1.0 bar to capture Ø 15 μm particles and Ø 7 μm particles. In the case of PC3 capture, we applied 0.02 bar and 1.2 bar for loading a cell suspension and actuating the valve. The process of particle capture and release was repeated more than 100 times to test the robustness of the system. During the processes, more than one particle or cell was captured from suspensions with high concentration. Still not a single particle or cell was not captured by the v-type valve. The applied pressures to capture Ø 15 μm and Ø 7 μm particles matched with the pressures to create valve openings smaller than 15 μm and 7 μm as is shown in the Table above. However, a higher pressure was required to generate a smaller valve opening to capture PC3 (having a characteristic size of about 15-16 μm)

cells as compared to the openings for particle capture. This can likely be contributed to the greater flexibility of cell membranes (see e.g. F. Coumans *et al.* (2013), PloS one **8**(4), p. e61770). Debris and damaged cells passed through the valve as their sizes were smaller than the opening area of the channel adjusted by the actuation of the valve.

Using the v-type valve we also were able to generate a solid phase column. Schematically the process of generation of a solid phase column in a fluidic channel is depicted in Fig. 9. We actuated the v-type valve with valve design #1 by applying 1.6 bar and loaded Source 15Q (Ø 15 µm particles for anion exchange) suspension. When the v-type valve was actuated the particles in the fluid flow of the suspension were sieved and packed and a packed column was configured upstream of the v-type valve. The packed particles were easily released by opening the valve. The process of packing and releasing particles could be repeated by controlling the v-type valve.

Isolation of a desirable number of particles in a reactor

To demonstrate the isolation of particles captured by a v-type valve in separate reactors for further analysis on or with the particles we designed a microfluidic device with isolation chambers in connection with a v-type valve. The photolithographic mask design is shown in Fig. 7a. The device consists of two main units, a capture unit and a chamber unit. In the capture unit a v-type valve is arranged at the intersection of two fluidic channels and two shut-off valves (on/off valves) are located at opposite sides of the intersection in each fluidic channel. A fluid flow in the fluidic channel could be completely blocked by closing the two shut-off valves in the channel and could be controlled in the direction of a fluid flow in the intersection by controlling the four shut-off valves.

The process of capture and pushing particles in a reactor is shown in figs 3a-3c and explained above in the detailed description of the embodiments. To evaluate the capability of the system for the isolation of a desirable number of particles in reactors we captured certain numbers of Ø 15 µm particles and pushed them in chambers in certain positions. The process was monitored using microscope images of isolated particles in chambers by bright field and fluorescent illuminations. The detailed operation is shown schematically in Fig. 7b. Experimentally we were able to capture and isolate one, two, three, four, and five particles in the first, second, third, fourth, and fifth chambers, respectively.

Sieving particles out of a droplet in the flow of two immiscible fluids

To demonstrate the feasibility of a v-type valve for sieving particles in two-phase droplet flows, we designed a droplet-based microfluidic device with a v-type valve. The device comprises a droplet generator, a sieving unit, and a separating unit. The droplet generator was designed to control the size of droplets by mechanical cutting of a flow of a dispensed phase by a shut-off valve according to Lee, *et al.* (2009), Microfluidics and nanofluidics 7(3), p. 431-438, and Zeng, *et al.* (2009), Lab Chip 9(10), p. 1340-1343. Using the droplet generator droplets of a Source 15Q suspension containing particles were generated in a carrier fluid comprising mineral oil. The formed droplets flowed into the sieving unit wherein the v-type valve is located When the v-type valve was actuated particles in droplets could be sieved in the valve area, while the droplet could pass the valve. The trapped particles could successively be released in a single droplet by opening the valve, as is schematically depicted in fig. 9.

Adsorption isotherm determination of bovine serum albumin

A processing device as described herein, see Fig. 6, comprising 18 reactors (flow channel systems) with substantially the same volume and dimensions was provided. All reactors were provided as a set of reactors (1a, 1b; 2a, 2b; …., 9a, 9b). A predefined fluorescein isothiocyanate labeled bovine serum albumin, FITC-BSA (pH 7.0) was directed to the reactors (all a ***and*** b reactors), and (only) the b-reactors (1b, 2b, 3b, …, 9b) were loaded with a number of "Source 15Q" (GE Healthcare) resin particles, wherein all b-reactors (1b, 2b, 3b, ..., 9b) were loaded with substantially the same number of the same resin particles and each set of reactors (1a+1b, 2a+2b, …, 9a+9b) was provided with the same concentration FITC-BSA, wherein the concentration of BSA in each reactor (i.e., the initial BSA concentration in solution, C_i for each reactor(set)) was selected to be different form the concentration in other sets. (Especially, 1a and 1b did not contain FITC-BSA / were provided with a concentration. of 0 mol/l FITC/BSA). Successively, the fluid in all reactors (and the particles in the b-reactors) were circulated in their respective reactor and after a period of 10 min. a steady state between BSA bound to the resin particles and BSA in solution was reached. After this period, the fluid (the protein solution) was removed from the reactors and the fluorescence intensity was determined for all reactors (a+b). The

amount of BSA bound to the resin in each reactor was determined from the difference in the fluoresce intensity between the b-reactor and the a-reactor for each set of reactors (1a+1b, 2a+2b, ... 9a+9b), therewith correcting for a decay in fluorescence intensity caused by degradation of the fluorescence and BSA bound to the walls of the channel system. From the amount of BSA bound to the resin and the number of resin particles (with known surface area per particle) the amount of BSA bound per m^2 of resin, C_B, was calculated and the adsorption isotherm giving C_B as a function of C_I could be generated .

REFERENCES

1	fluidic device	41	first valve section
10	fluid flow channel	42	second valve section
11	first fluid flow channel	45	second fluid flow direction system
12	second fluid flow channel	100	processing device
13	control channel	110	(particle) introduction system
14	intersection	120	flow channel system
15	control layer	125	(processing device) chamber
16	flow layer	126	analysis system
17	membrane	130	detection system
18	channel axis	140	control system
19	cross sectional area	145	connecting wire
2	Particle	150	restriction element
3	valve	151	filter
31	v-valve	180	column (packed bed)
32	on/off valve	181	column support
33	set of valves configured as a pump	200	multichannel system microfluidic device
35	effective passageway area	310	first fluid
36	first channel valve	320	second (immiscible) fluid
37	second channel valve	325	droplet
38	upstream side of the valve		
39	downstream side of the valve		

l	length of the valve
l_1	first section length
l_2	second section length
w	(adjustable) valve width, i.e. width of the first fluid flow channel at the intersection

CLAIMS:

1. A fluidic device (1) having a particle trap functionality for a particle (2) in a fluid, the fluidic device (1) comprising a first fluid flow channel (11), a second fluid flow channel (12), and a control channel (13), wherein the first fluid flow channel (11) is in fluid contact with the second fluid flow channel (12) and intersects the second fluid flow channel (12) at an intersection (14), wherein the control channel (13) at the location of the intersection (14) is arranged adjacent to the first fluid flow channel (11) and separated by a flexible membrane (17) from the intersection (14), wherein the flexible membrane (17) is configured as a valve (31), configurable in operation at a first pressure in the control channel (13) in a first position not to block propagation of a particle (2) of a predetermined size in the first fluid flow channel (11), and at a second pressure in the control channel (13) in a second position to block with said flexible membrane (17) propagation of said particle (2) through the first fluid flow channel (11), while in this second position not fully blocking fluid flow through the first fluid flow channel (11), wherein the valve (31) is configured to provide in said second position a gradual increasing blockade of a cross sectional area (19) of the first fluid flow channel (11) in a direction parallel to a longitudinal axis of the first fluid flow channel (11).

2. The fluidic device (1) according to claim 1, wherein the first fluid flow channel (11) at a location of the valve (31) comprises an effective passageway area (35), wherein in the second position (of the membrane) a first effective passageway area at the upstream side of the valve (31) is larger than a second effective passageway area at a location further downstream from the first effective passageway area, wherein the second effective passageway area (35) at a first pressure in the control channel (13) is larger than the second effective passageway area (35) at a second pressure in the control channel (13) if the second pressure is larger than the first pressure.

3. The fluidic device (1) according to any one of the preceding claims, having a controllable pressure in the control channel (13).

4. The fluidic device (1) according to any one of the preceding claims, wherein further two first channel valves (36) are provided in the first fluid flow channel (11) and two second channel valves (37) are provided in the second fluid flow channel (12), wherein the two first channel valves (36) are each provided at opposite sides of the intersection (14) configured to allow complete blockage of the first fluid flow channel (11) at both sides of the intersection (14) and the two second channel valves (37) are each provided at the opposite site of the intersection (14) configured to allow complete blockage of the second fluid flow channel (12) at both sides of the intersection, and wherein during operation a fluid flow through the first and second fluid flow channels (11,12) can be controlled by controlling the first and second channel valves (36,37).

5. A processing device (100) comprising (i) a fluidic device (1) according to any of the preceding claims 1-4, (ii) an introduction system (110) configured to provide a fluid flow with one or more particles (2) into the first fluid flow channel (11), (iii) a flow channel system (120), in fluid contact with the second fluid flow channel (12), comprising a chamber (125), configured for performing a process wherein a particle (2) is used, wherein the process is selected from a chemical process, a biochemical process, physical process, and an analytical process, (iv) an analysis system (126) configured to analyze a parameter of the process, and optionally (v) a detection system (130) configured to detect a presence of a particle (2) at the intersection (14) of the first fluid flow channel (11) and the second fluid flow channel (12), and (vi) a control system (140) at least configured to control the fluidic device (1) and the introduction system (110).

6. The processing device (100) according to claim 5, wherein during operation the fluidic device (1) is controllable to load a particle (2) in the flow channel system (120).

7. The processing device (100) according to any one of the preceding claims 5-6, wherein the processing device (100) comprises a detection system (130), and wherein the fluidic device (1) is configured to load the particle (2) in the flow channel system (120) when a particle (2) is detected by the detection system (130).

8. The processing device (100) according to any of the preceding claims 5-7, wherein a predetermined number of particles (2) are loaded in the flow channel system (120).

9. The processing device (100) according to any of the preceding claims 5-8, comprising a number of particles (2) loaded in the in the chamber (125), wherein the number of particles provide a column (180) comprising particles (2) configured for performing the process.

10. The processing device (100) according to any of the preceding claims 5-9 comprising a plurality of flow channel systems (120) in fluid contact with the second fluid flow channel (12), wherein the processing device further comprises a second fluid flow direction system (45) configured to control the fluid flow in the second fluid flow channel (12) to each of the plurality of flow channel systems (120).

11. The processing device (100) according to claim 10 comprising the detection system (130) configured to detect the presence of a particle (2) at the intersection (14) of the first fluid flow channel (11) and the second fluid flow channel (12).

12. A method for performing a batch adsorption experiment for determining an adsorption characteristic of a molecule to a particle (2), the method comprising:

- providing the processing device (100) according to claim 11;

- loading a determined number of particles (2) in the plurality of flow channel systems (120) providing particle loaded flow channels systems (120);

- loading molecules in the plurality of flow channel systems with different concentrations of the molecule in the flow channel systems (120); and

- determining the adsorption characteristic on the basis of the content of non-adsorbed molecules in the respective flow channel systems (120) and/or on the basis of adsorbed molecules in the respective flow channel systems (120).

13. The method according to claim 12, wherein the molecule is a protein, wherein the particle (2) comprises a resin particle having a diameter selected from the range of 0.1–50 μm, and wherein the adsorption characteristic is an adsorption isotherm.

14. Use of the fluidic device (1) according to any one of claims 1-4 or the processing device (100) according to any one of claims 5-11, for pH-gradient chromatofocusing, adsorption, desorption, chromatography, or pharmaceutical applications.

15. The use according to claims 14, for performing a batch adsorption experiment.

16. A method of controlling a flow of a particle (2) in a fluidic device (1) according to any one of the preceding claims 1-4, the method comprising flowing a fluid comprising the particle (2) through a fluid flow channel (11,12), trapping the particle (2) at the intersection (14), and flowing a fluid comprising said particle (2) through the other fluid flow channel (12,11).

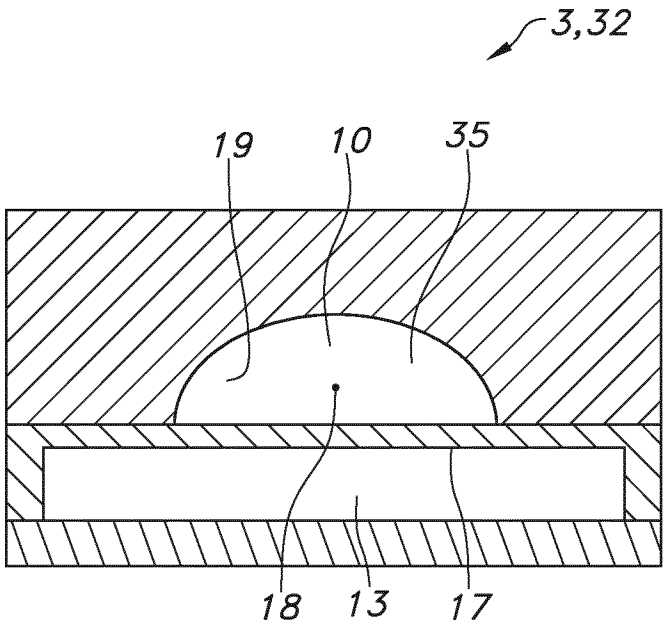


FIG. 1A

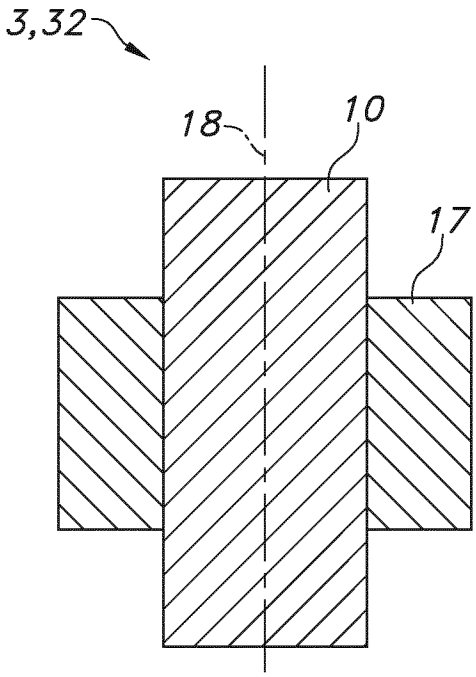


FIG. 1B

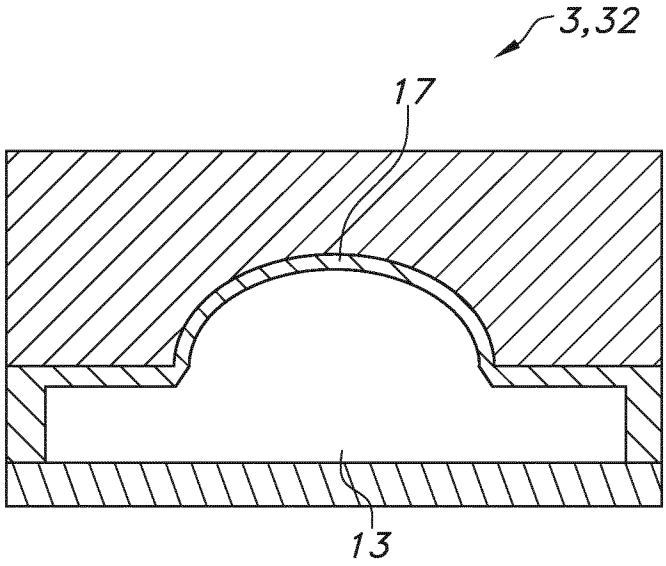


FIG. 1C

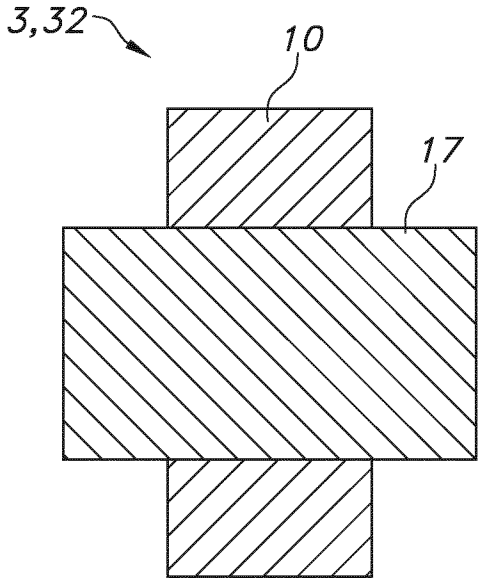
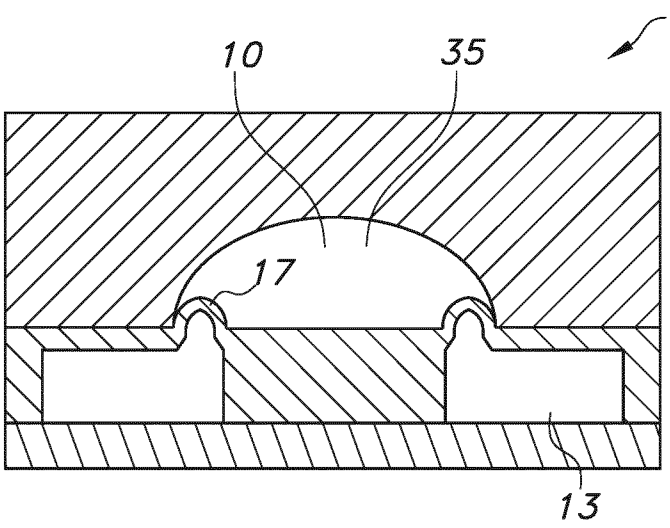
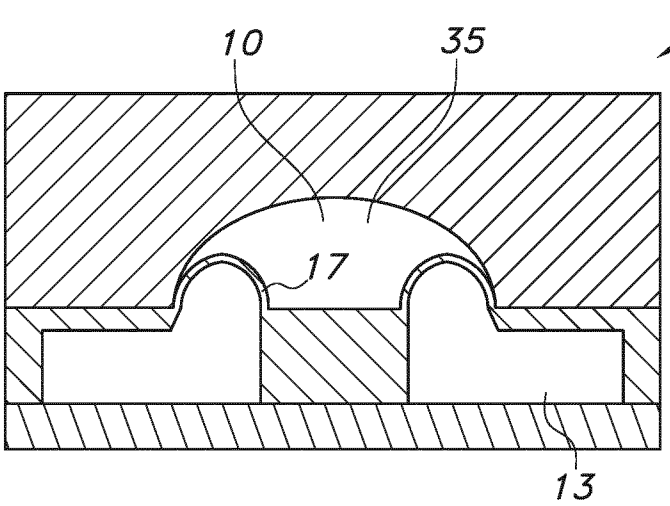


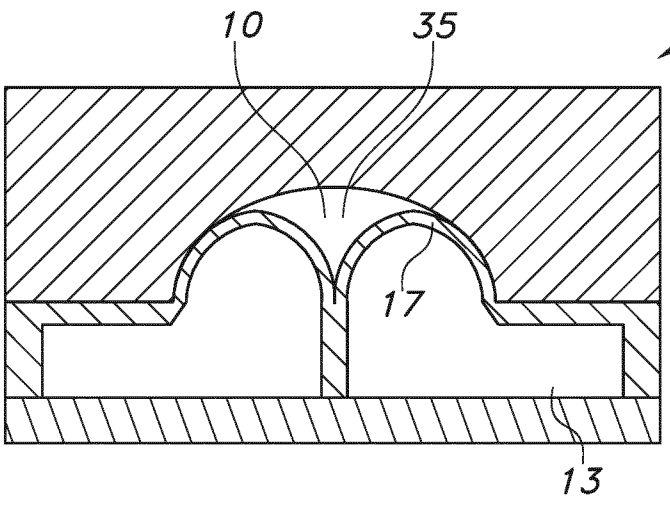
FIG. 1D



A-A
FIG. 2A



B-B
FIG. 2B



C-C
FIG. 2C

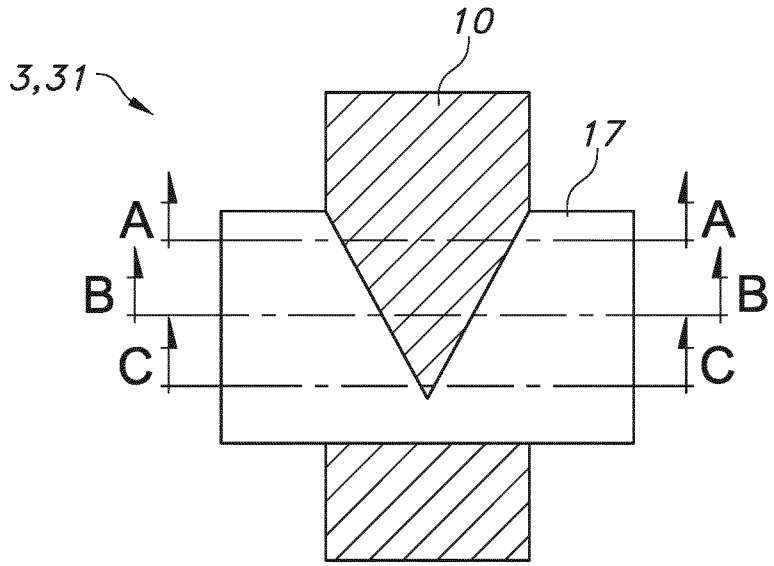


FIG. 2D

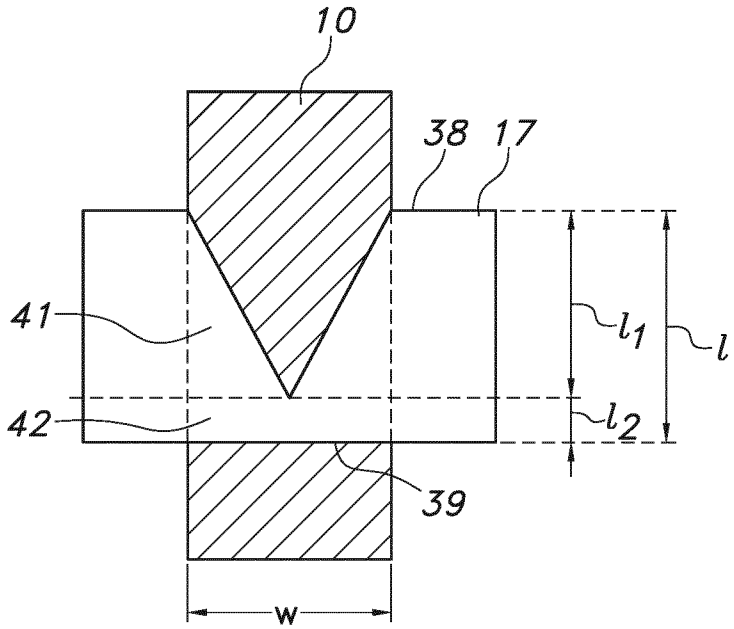


FIG. 2E

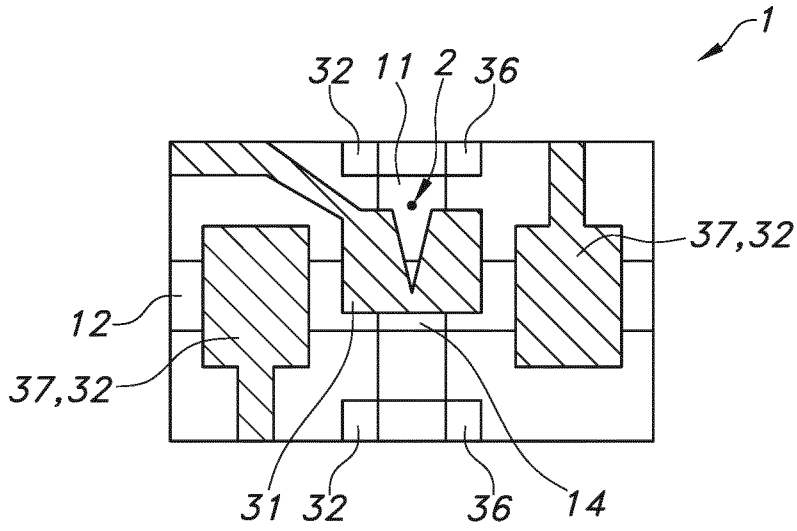


FIG. 3A

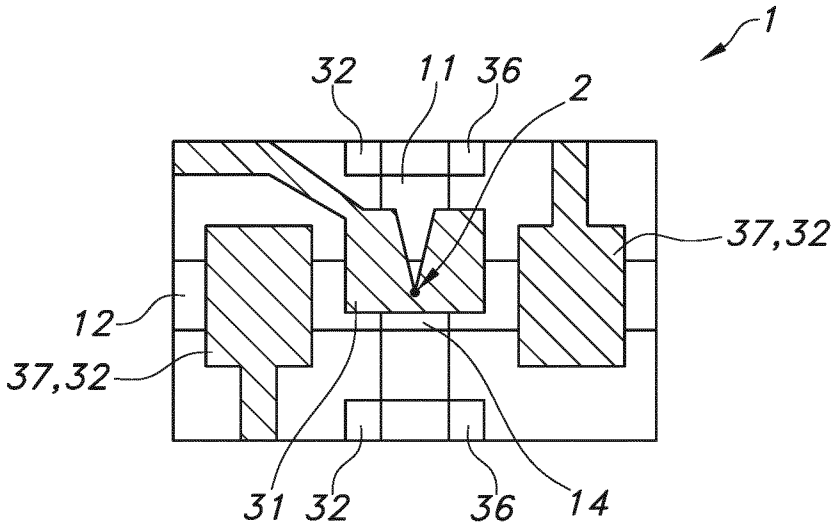


FIG. 3B

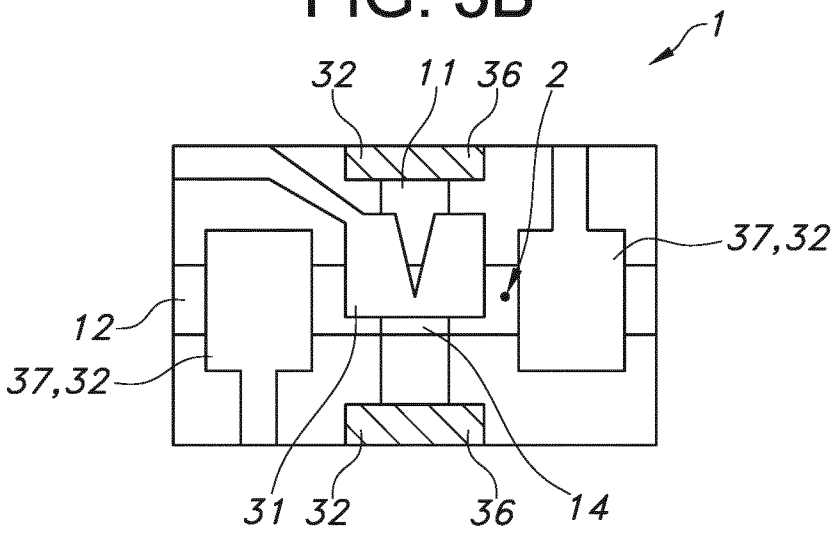
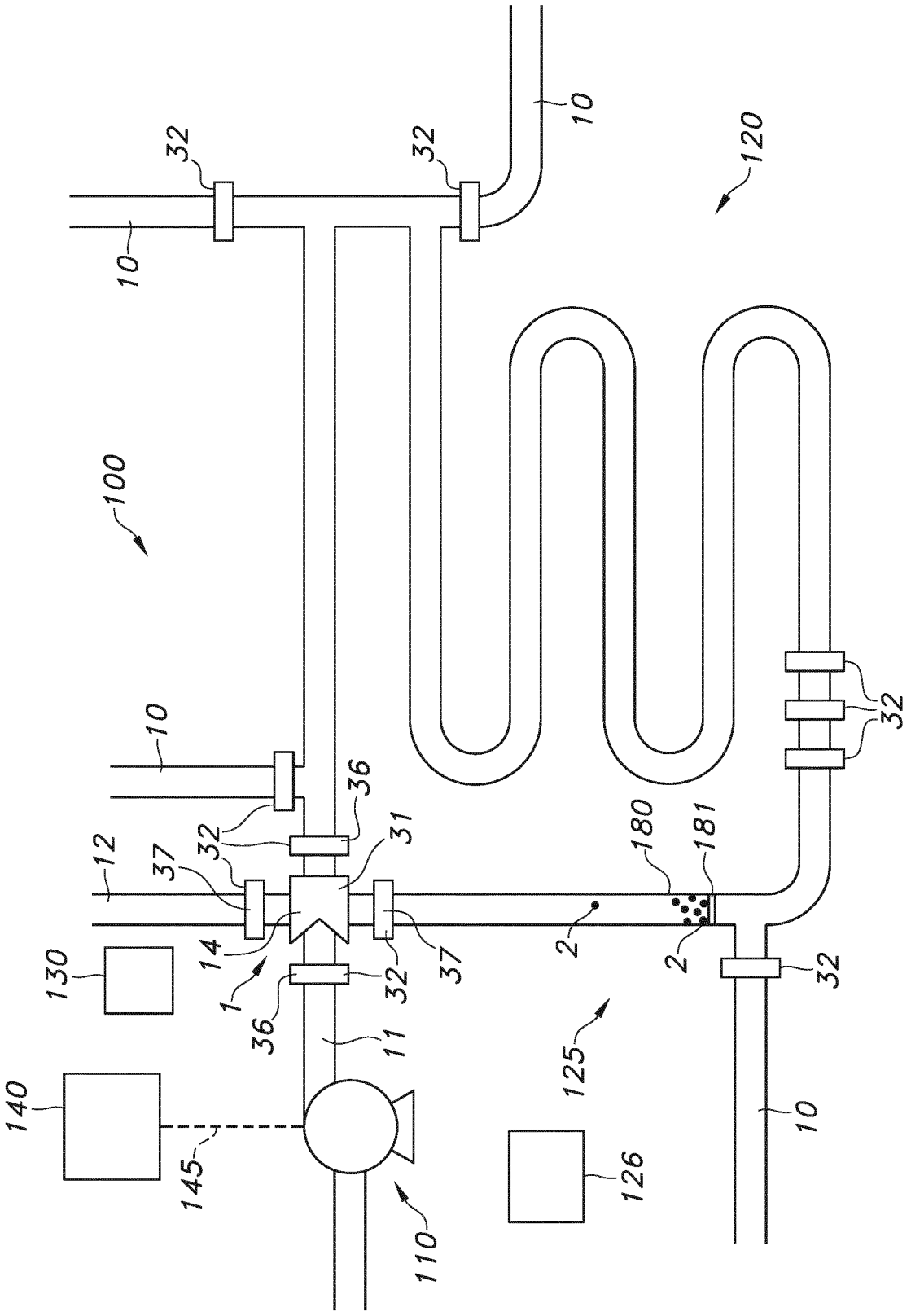


FIG. 3C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181
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FIG. 4

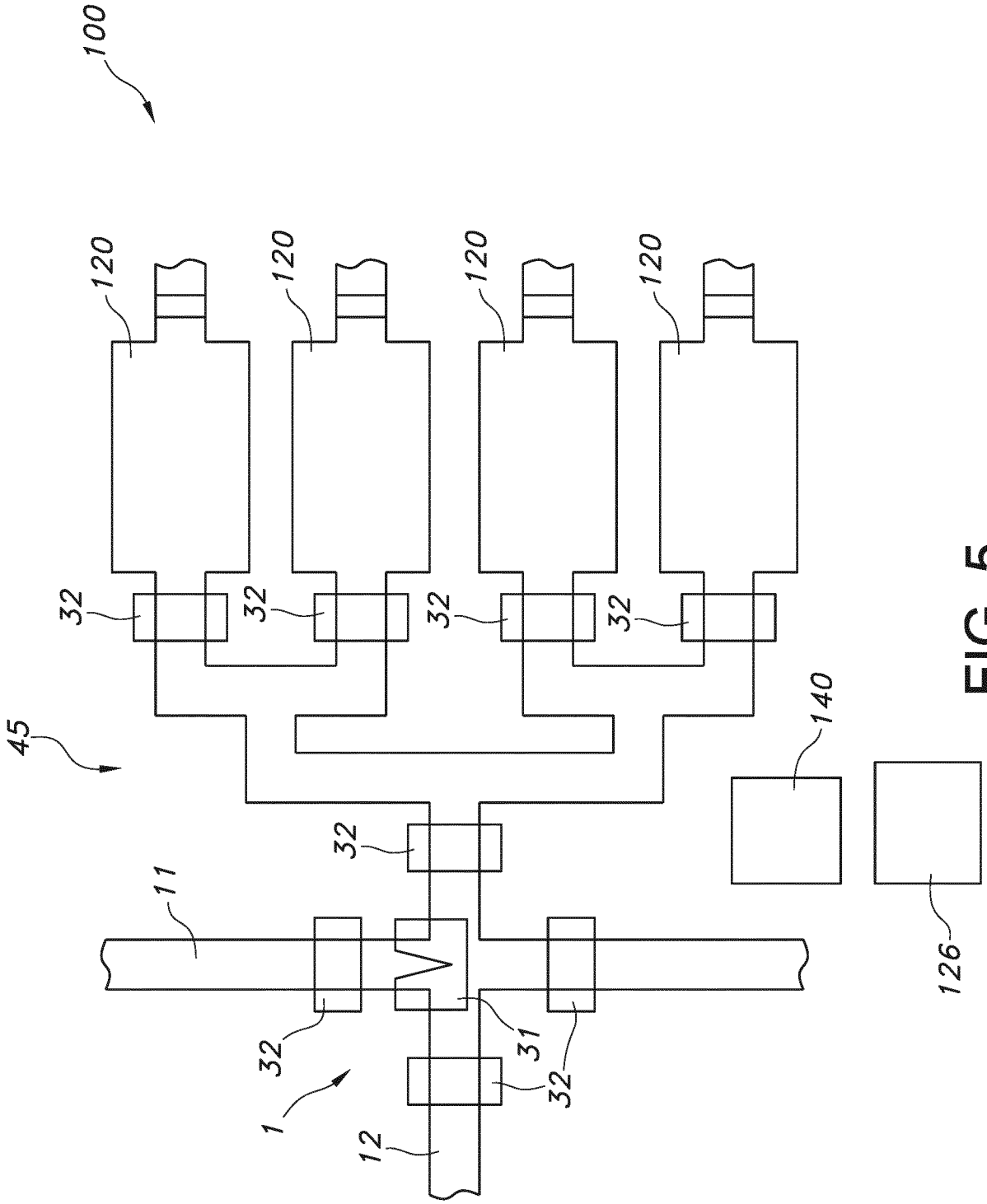
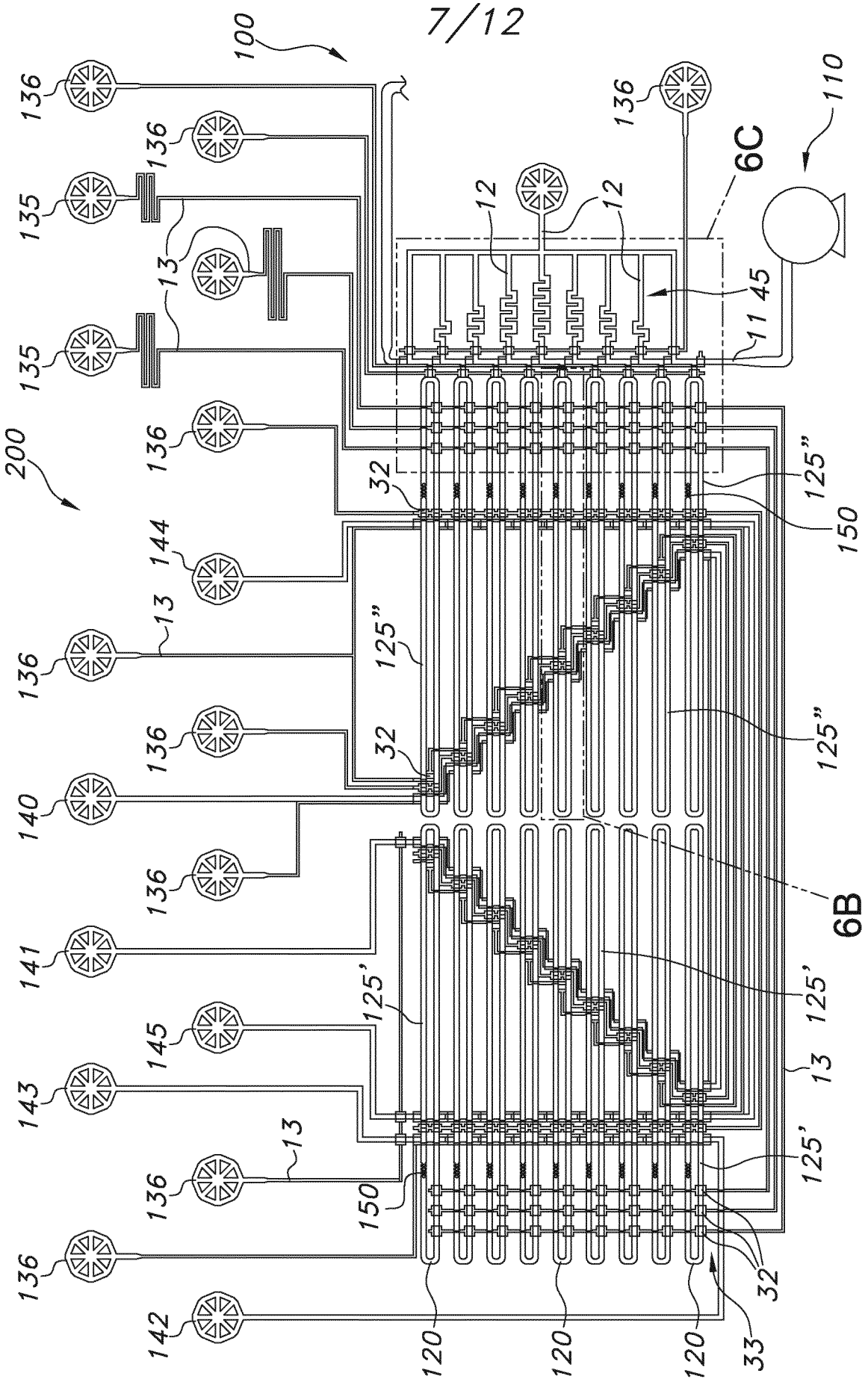


FIG. 5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6B
6C
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FIG. 6A

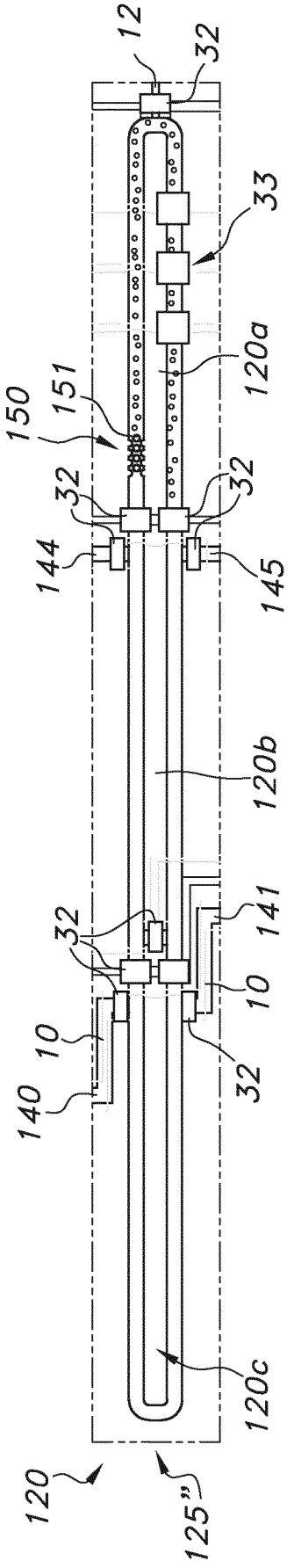
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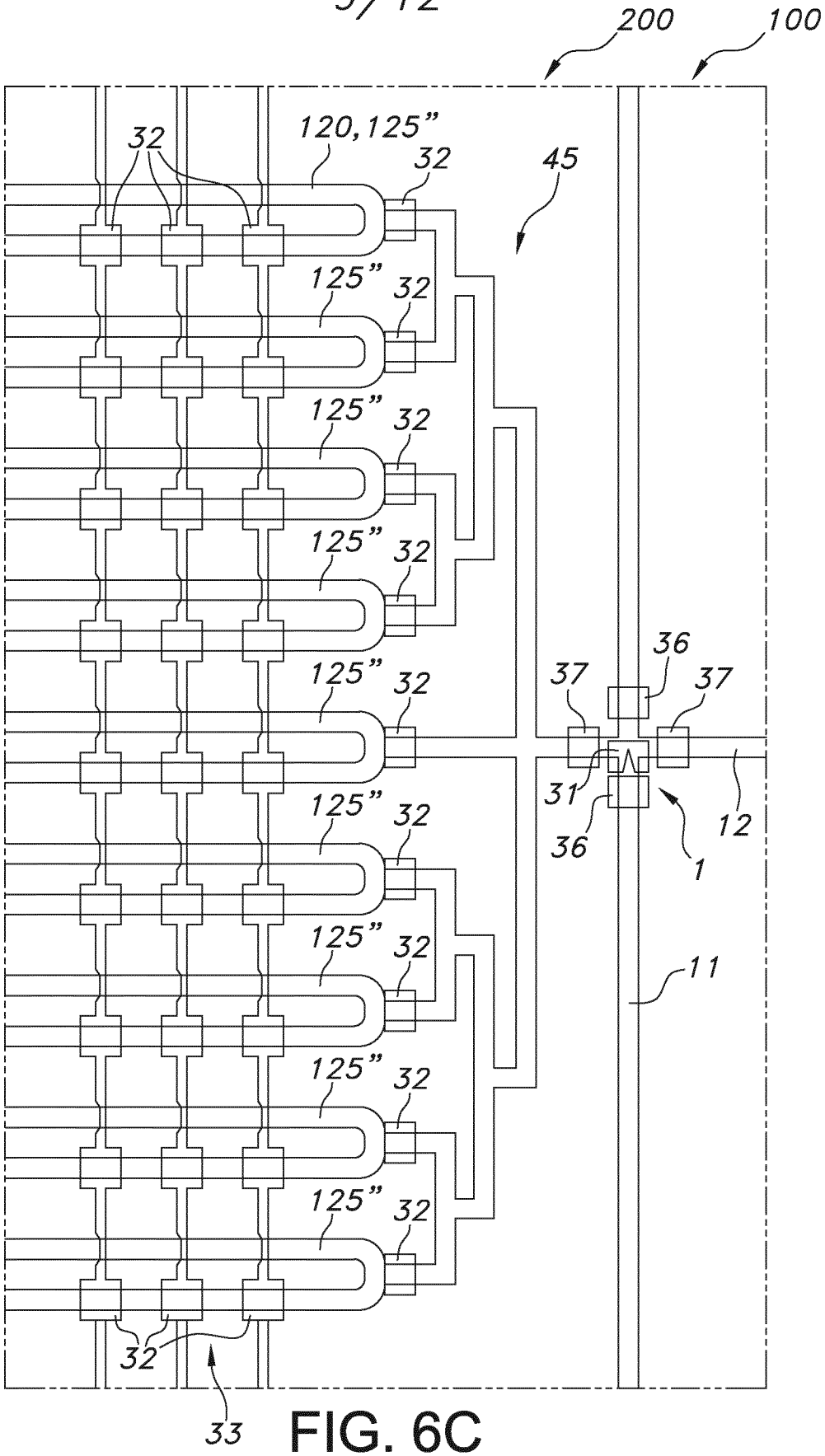
FIG. 6B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120,125"
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11
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32
125"
32
32
33

FIG. 6C

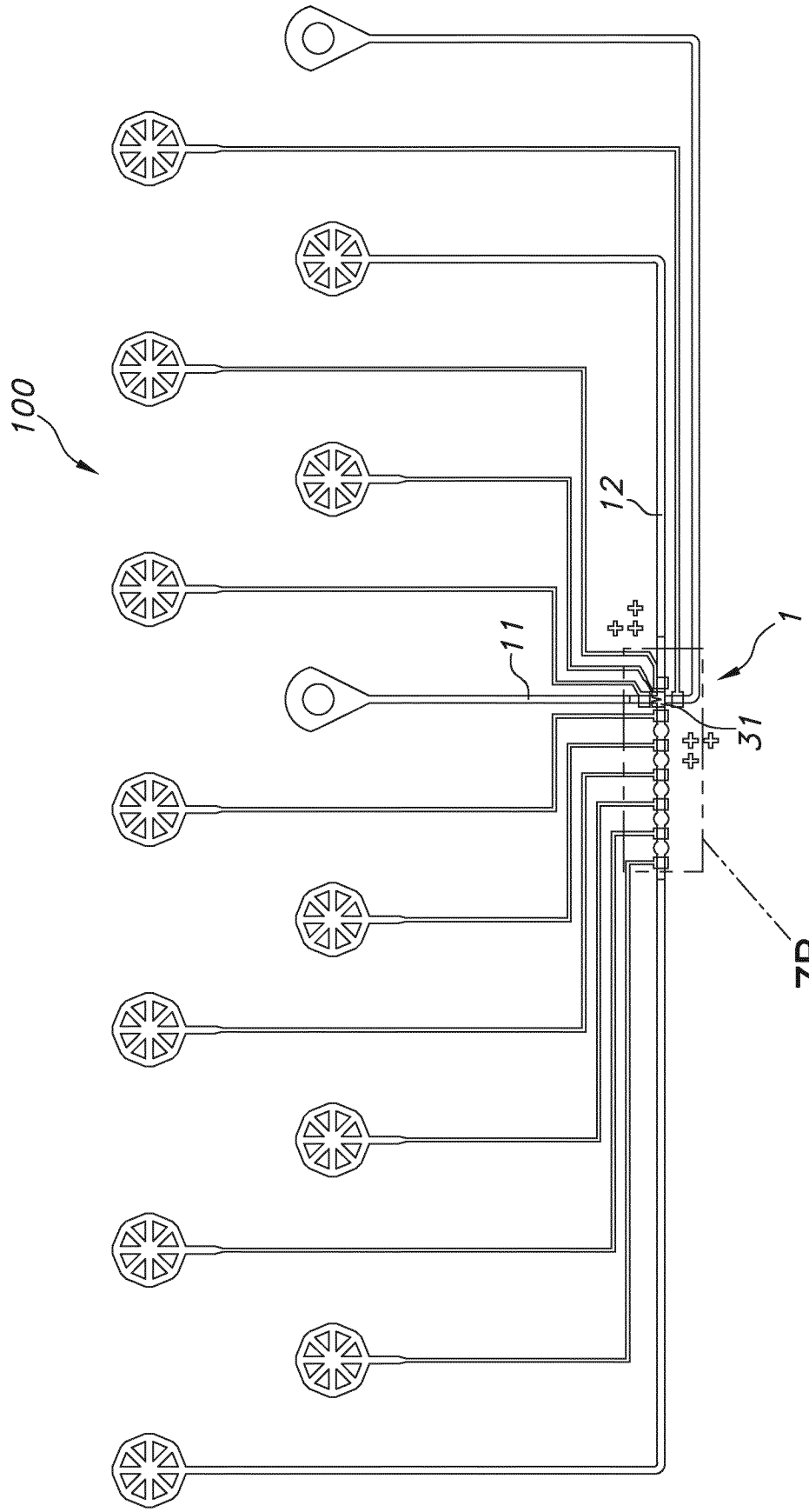

FIG. 7A

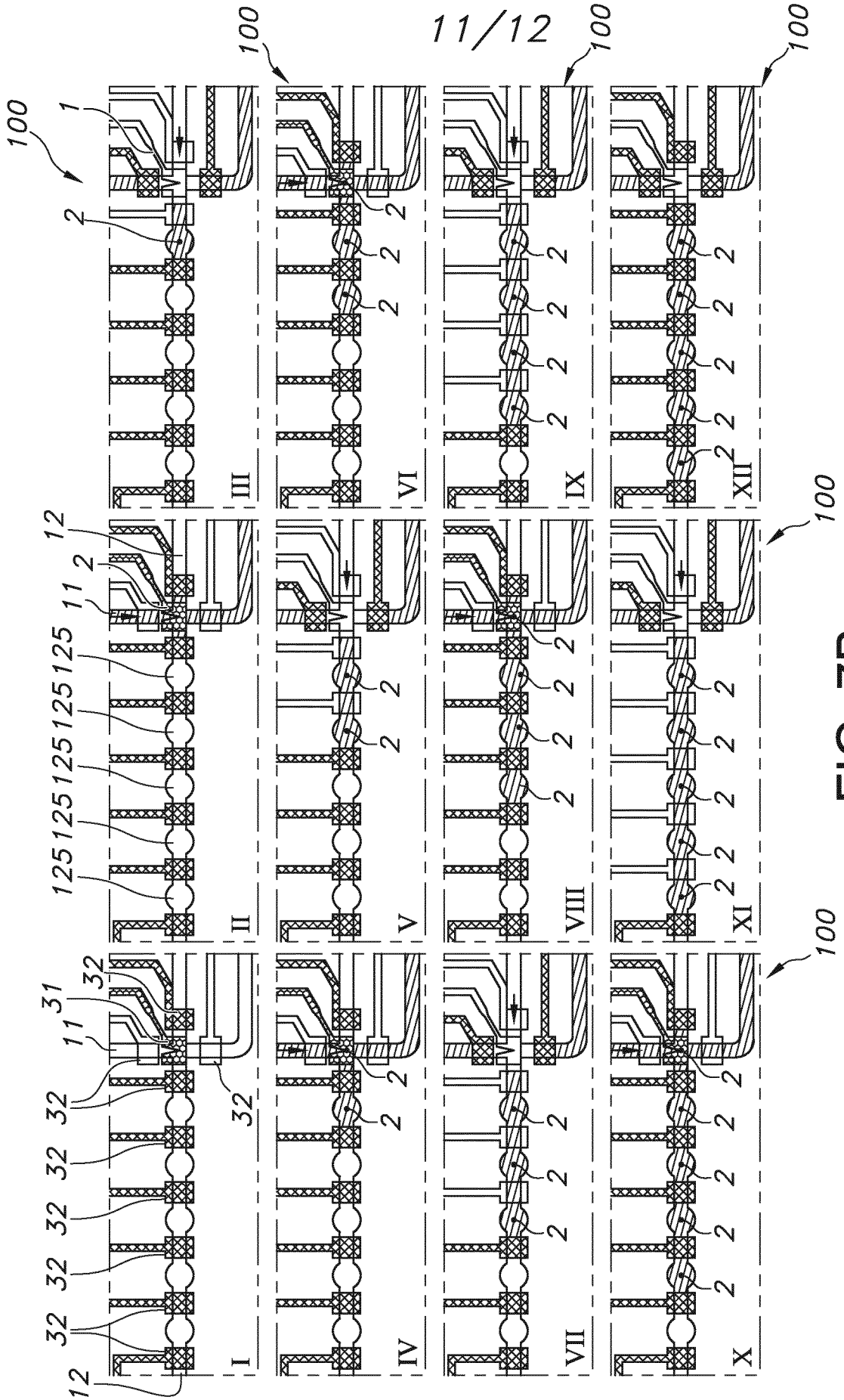

FIG. 7B

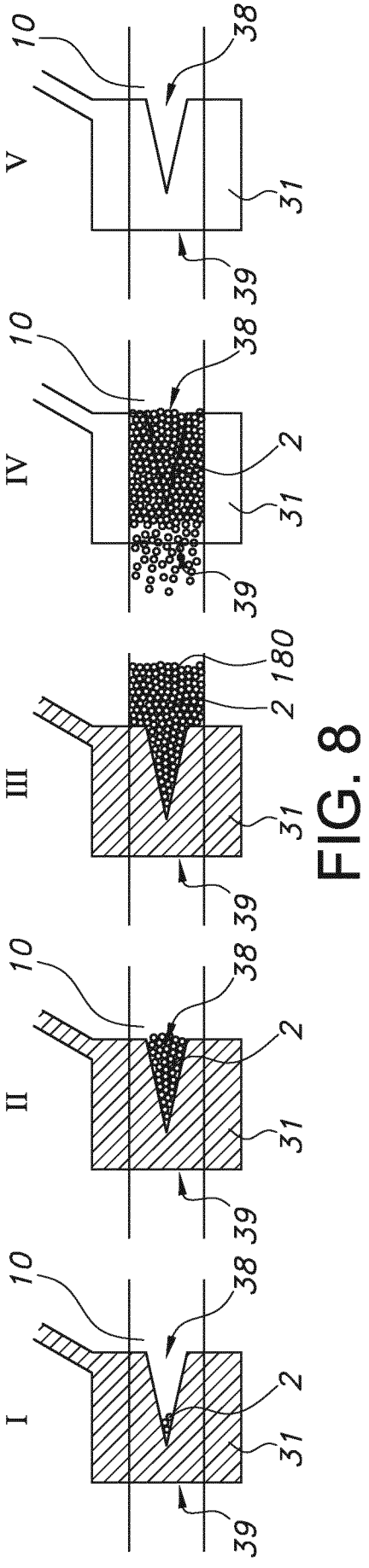

FIG. 8

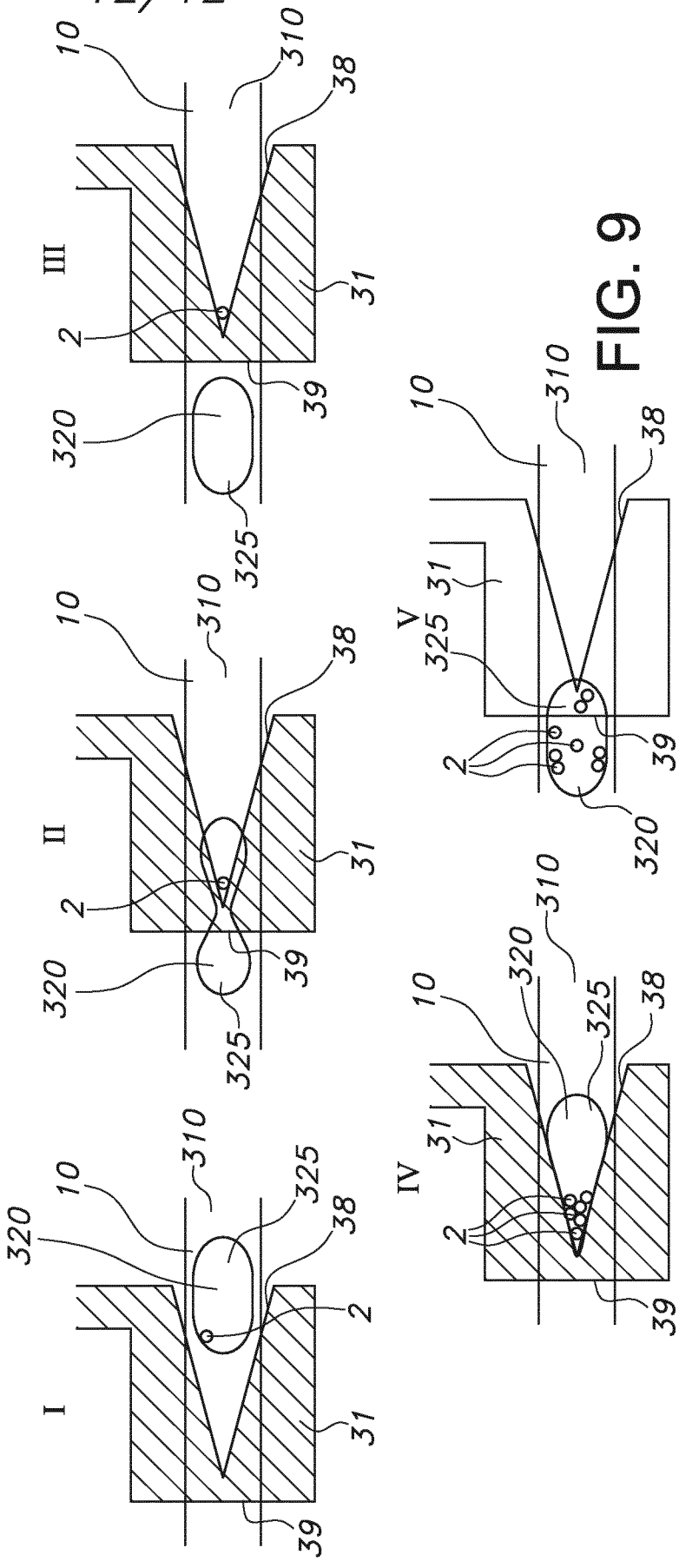

FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/064621

A. CLASSIFICATION OF SUBJECT MATTER
INV. F16K99/00 G01N30/60 B01L3/00
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)
F16K G01N B01L

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	US 2014/034556 A1 (MA HONGSHEN [CA] ET AL) 6 February 2014 (2014-02-06) paragraphs [0052] - [0106]; figures 1-9	1-16
A	US 2011/030808 A1 (CHIOU PEI-YU [US] ET AL) 10 February 2011 (2011-02-10) paragraphs [0042], [0067] - [0070]; figures 2,3,20,21	1-16
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X	US 2002/127736 A1 (CHOU HOU-PU [US] ET AL) 12 September 2002 (2002-09-12) paragraph [0198]; figure 19	1-11

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 September 2016	28/09/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tiede, Ralph

3

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 2014/378352 A1 (DARIDON ANTOINE [US]) 25 December 2014 (2014-12-25) paragraphs [0454] - [0457]; figures 18-20	1-16

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Information on patent family members

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