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(72) PETERS, RALPH-PETER, DE
(71) MICROPARTS GESELLSCHAFT FÜR MIKROSTRUKTURTECHNIK MBH, DE

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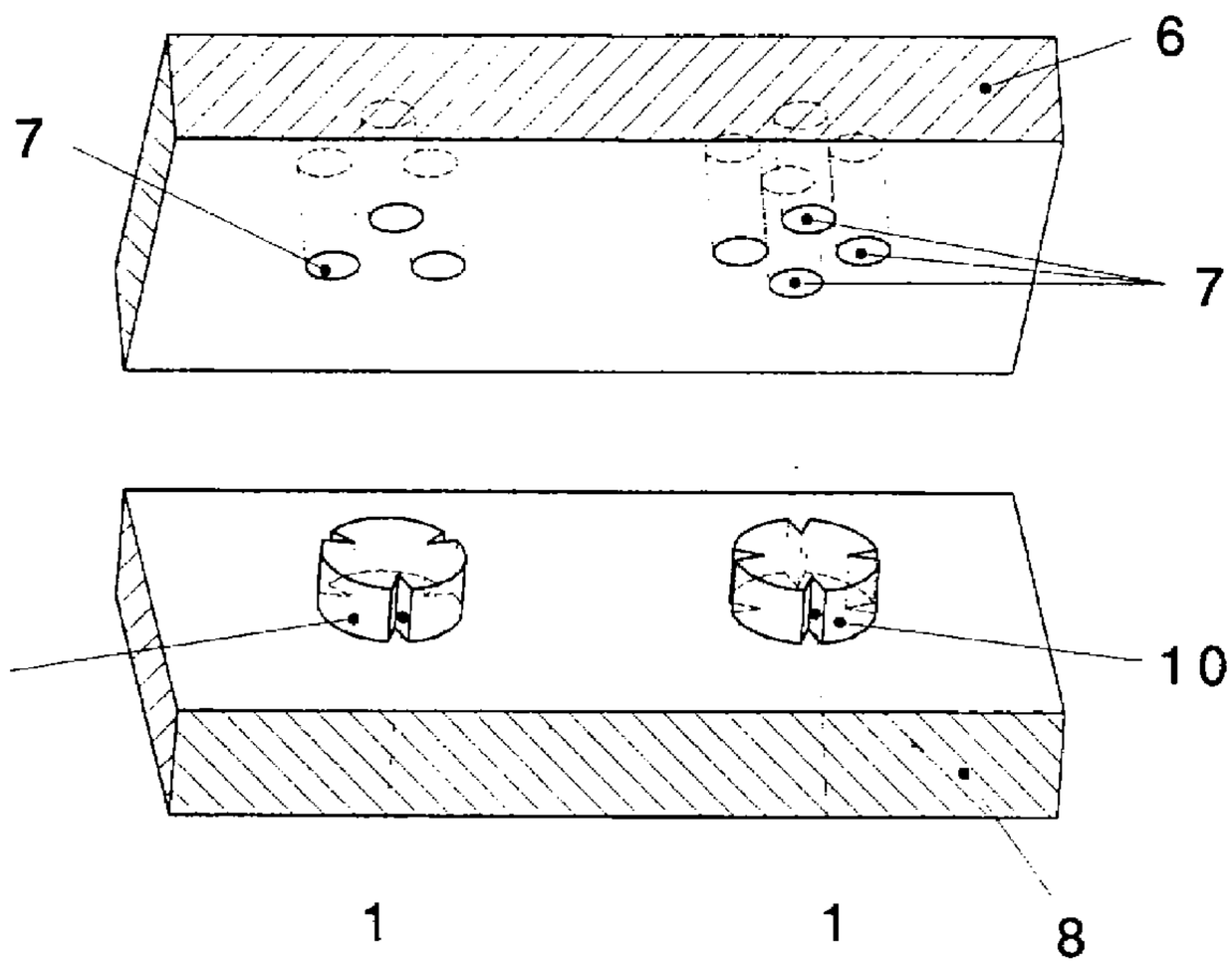
(54) **DISPOSITIF POUR ELIMINER UN LIQUIDE DE CAPILLAIRES**
(54) **DEVICE FOR REMOVING A LIQUID FROM CAPILLARIES**



(57) Liquid components are separated from a liquid using separation devices, such as filters and membranes, in which capillary forces which retain the liquid component to be separated off in the separation device are effective. If the amount of liquid is only small, it can be very difficult to remove the liquid component to be separated off from the separation device in free and unchanged form. This process step is simplified or facilitated by a wedge-shaped cut-out at the exit end of the capillary or in a columnar body which is in contact with the exit end of the capillary. The radius of curvature of the wedge edge is smaller than the radius of the capillary. The base side of the wedge-shaped cut-out is adjacent to a collecting chamber, in which the separated-off liquid component is collected, and in which the capillary forces are smaller than in the capillary. If interfering capillary forces are still effective in the collecting chamber, a further wedge-shaped cut-out can be provided at the exit end of the collecting chamber. The device makes it possible to separate off liquid components in the microlitre range.

Abstract

Liquid components are separated from a liquid using separation devices, such as filters and membranes, in which capillary forces which retain the liquid component to be separated off in the separation device are effective. If the amount of liquid is only small, it can be very difficult to remove the liquid component to be separated off from the separation device in free and unchanged form.

This process step is simplified or facilitated by a wedge-shaped cut-out at the exit end of the capillary or in a columnar body which is in contact with the exit end of the capillary. The radius of curvature of the wedge edge is smaller than the radius of the capillary. The base side of the wedge-shaped cut-out is adjacent to a collecting chamber, in which the separated-off liquid component is collected, and in which the capillary forces are smaller than in the capillary. If interfering capillary forces are still effective in the collecting chamber, a further wedge-shaped cut-out can be provided at the exit end of the collecting chamber.

The device makes it possible to separate off liquid components in the microlitre range.

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The invention relates to a device for removing a wetting liquid from one or more capillaries.

The purpose of the invention is to simplify the removal of a liquid from capillaries or to enable the liquid to be obtained as a free-flowing liquid.

Capillaries are narrow spatial structures in which surface effects of liquids occur. They can have any cross-sectional shape, including tubes and gaps. The dimensions of the cross section are in the millimetre to sub-micron region in at least one direction. The capillaries can have any desired spatial course.

Capillaries can exist as discrete structures in the form of individual straight or bent tubes having a relatively thin wall, or they can be in the form of a tube passing through a body. Furthermore, they can be pores in an open-pore porous body or a sintered body or in the form of spaces between closely packed fibres in the form of paper, nonwovens or felt. They can furthermore have the shape of narrow gaps.

The surface of a wetting liquid adjoining a solid wall forms a contact angle of from 0 degrees to less than 90 degrees with the wall; incompletely wetting liquids have a contact angle which is greater than zero. Owing to their surface tension, wetting liquids are drawn into capillaries until the latter are completely filled. If a small force acts on the liquid at the exit end of the capillaries, the surface tension can hold the liquid in the capillaries and prevent it from exiting. However, the liquid can be forced to exit from the end of the capillaries by means of a sufficiently large pressure difference in the liquid between capillary entrance and capillary exit.

EP 0 336 483 discloses a device for separating an initially introduced liquid, which device consists of a first open-pore membrane (separator membrane) and a second open-pore membrane (collector membrane), where the collector membrane is directly adjacent to the exit side of the separator membrane. The part of the liquid introduced on the one side of the separator membrane that has passed through

the separator membrane enters the collector membrane, where it remains. The liquid collected in the collector membrane above the separator membrane can be reacted with a reagent applied to the collector membrane, or the collected liquid can be washed out of the collector membrane by means of a further liquid and subsequently analyzed. The liquid separated off by means of the separator membrane and collected in the collector membrane can thus remain in the collector membrane during its further analysis or it can be washed out, in which case it is mixed with a further liquid. In neither case is a free-flowing liquid obtained that consists of only the part of the initially introduced liquid that has been separated off by means of the separator membrane.

For the analysis or use of liquids which have been collected with the aid of capillaries or separated off from a liquid medium, it may be advantageous or necessary to obtain the liquid from the capillaries as a free-flowing liquid which is not mixed with any further liquid.

The object is thus to indicate a device by means of which the liquid can be removed from one or more capillaries and collected in a collecting chamber as a free-flowing liquid. In a sufficiently large collecting chamber, surface effects are virtually no longer effective.

The invention provides a device for removing a liquid from at least one capillary into a collecting chamber comprising: a structure that defines a capillary passage having an exit end, and a wedge-shaped cut-out at said exit end; said wedge-shaped cut-out having: a root formed by a wedge edge that defines a radius of curvature which is smaller than half the smallest dimension of said capillary passage, and a wedge angle between wedge surfaces of the cut-out of less than 150 degrees; and a collecting chamber adjacent to a lower end of the wedge-shaped cut-out.

In the case of capillaries having any desired cross section, but whose dimensions are in the same order of magnitude in two mutually perpendicular directions, the radius

of curvature of the wedge edge (i. e. the root of the wedge-shaped cut-out) is smaller than the equivalent radius of the non-circular capillary. The equivalent radius of a capillary having a non-circular cross section is the radius of a circle whose area is identical to the area of the non-circular cross section of the capillary. In the case of capillaries which are in the form of pores in an open-pore body, the cross-sectional area of the capillaries is distributed over the cross section region. In this case, the radius of curvature of the wedge edge is smaller than half the smallest dimension of the capillary having the largest cross section. In the case of slot-shaped capillaries, the radius of curvature of the wedge edge is smaller than half the thickness of the slot.

The wedge edge or root is adjacent to the two wedge surfaces of the cut-out, which form a wedge that is preferably less than 90 degrees, with one another. The wedge surfaces of the cut-out can be rounded off in a convex manner in the region of the base side.

The device according to the invention can be in the form of a one-piece body or can be composed of two parts.

In the two-piece design, the at least one capillary is located in the first body. The second body consists of a base plate which is provided on one side with preferably a plurality of projections. At least one wedge-shaped cut-out is present in at least one of these projections. A projection can be provided with a plurality of wedge-shaped cut-outs, each of which is assigned to at least one capillary. The free end of the at least one projection is in contact with the surface of the first body, in which the exit end of the at least one capillary is located. The beginning of the root or wedge edge of the wedge-shaped cut-out lies within the exit area of the capillary. Any small separation which may be present between the first body and the free end of the projections of the second body has no effect on the action of the device according to the invention, so long as the liquid present at the exit ends of the capillaries in the first body is in contact with the free end of a projection of the second body.

The collecting chamber is provided in the vicinity of the wedge-shaped cut-outs provided in the projections. This collecting chamber is essentially limited by the side of the base plate on which the projections are provided and by the side of the first body in which the exit areas of the capillaries are located.

In the two-piece design, the first body can contain a single capillary or a plurality of individual capillaries. The first body can furthermore be an open-pore membrane or an open-pore sintered body, or it can consist of fibres, such as a nonwoven, a felt or paper, for example blotting paper. Bodies of this type preferably have a planar exit side. In the latter case, it is sufficient to bring the free ends of projections containing at least one wedge-shaped cut-out into contact with the exit side of the open pores in the first body. Owing to the multiplicity of randomly distributed pores, which are generally interconnected within a body of this type, the position of the beginning of the wedge edge at the free end of the projections can be selected virtually freely so long as a sufficiently large number of wedge-shaped cut-outs is present.

In the two-piece design of the device according to the invention, the wedge-shaped cut-outs which are present in the projections on one side of the second body, have roots as wedge edges that extend perpendicular to the surface of the first body in which the exit ends of the capillaries are located (angle between wedge edge and the surface of the first body equal to 90 degrees) or are inclined to this side surface by an angle of at least 20 degrees.

The projections can have the shape of columns, cones, pyramids or cross pieces arranged in island-like manner. The cross pieces can be straight or curved and can be provided on one or both sides with wedge-shaped cut-outs.

The one-piece design contains at least one capillary and a collecting chamber into which the capillary runs. At the exit side of the capillary, a wedge-shaped cut-out is present in the wall of the collecting chamber. The beginning

of the root or wedge edge of the wedge-shaped cut-out is in the wall of the capillary in the vicinity of its exit end.

If surface effects and capillary forces are effective in the collecting chamber in which the

liquid removed from the capillaries is initially collected, the device according to the invention, which consists of at least one capillary, at least one wedge-shaped cut-out and at least one collecting chamber, can have a number of wedge-shaped cut-outs and collecting chambers arranged one after the other until virtually no surface effects are effective in the last of a plurality of collecting chambers. In the case of a plurality of collecting chambers arranged one after the other – regarded in the flow direction of the liquid – the capillarity-determining dimensions of the second collecting chamber are larger than the capillarity-determining dimensions of the first collecting chamber, and the capillarity-determining dimensions of the third collecting chamber are larger than the capillarity-determining dimensions of the second collecting chamber.

The action of the device according to the invention is based on the suction action of the wedge-shaped cut-outs having the stated dimensions and in the stated arrangement on wetting liquids which are present at the wedge-shaped cut-outs, and on the reduction of surface effects in the collecting chamber, the surface effects in the collecting chamber being reduced, if necessary, to an insignificant level by multiple arrangement of the device according to the invention.

The device according to the invention is effective continuously so long as liquid is present at the beginning of the wedge edge and the collecting chamber is covered only on its base with a liquid layer in the vicinity of the wedge-shaped cut-outs and no liquid is present above this up to the height of the beginning of the weight edge of the wedge-shaped cut-out.

The device according to the invention has the following advantages:

- When the device is used, a free-flowing liquid is obtained which is located in a collecting chamber and is not held in a collector membrane.
- The free-flowing liquid is not mixed with another liquid.
- It enables the collection of a free-flowing liquid down into the microlitre region.
- It is effective independently of gravity, and the wedge edge can have any desired spatial direction.

The device according to the invention can consist of plastic, for example poly(methyl

methacrylate) (PMMA), polycarbonate (PC), polystyrene (PS) or the like, or metal, for example nickel, copper, cobalt, steel and alloys thereof, or a semiconductor, for example silicon or germanium.

The geometrical microstructures can be produced, for example, by deep X-ray lithography, UV lithography, fine-mechanical precision machining, laser treatment, dry etching or wet etching.

They can initially be produced in a plastic and converted into a complementary metal structure by electrodeposition of metal. This complementary structure can be used as a mould insert by means of which many of the desired plastic microstructures are cast with the aid of injection moulding.

Furthermore, a microstructure which is complementary to the desired microstructure can be produced in plastic, from which the desired metallic microstructure is cast by electrodeposition of metal.

The device according to the invention can be used, inter alia, for separating a liquid from a solid-containing medium by means of a filter membrane, for separating blood plasma from whole blood by means of a separator membrane or for filling the wells of a microtitre plate via a feed capillary.

The device according to the invention is explained in greater detail with reference to the Figures. Figures 1 to 4 relate to a two-piece device composed of two bodies, while Figures 5 and 6 relate to a one-piece device. Figures 7 and 8 show a two-piece device in which three collecting chambers with the associated wedge-shaped cut-outs are arranged one after the other.

Figure 1a shows a columnar projection (2) having a circular cross section and four wedge-shaped cut-outs (1) on a base plate (8). Figure 1b shows a columnar projection (3) having an irregular triangular cross section and four wedge-shaped cut-outs (1). Figure 1c shows a section of a projection (4) in the form of a cross piece with a plurality of wedge-shaped cut-

outs (1) on one side thereof.

Figure 2a shows a columnar projection (5) having a rectangular cross section and two wedge-shaped cut-outs (1). Figure 2b shows details of the wedge-shaped cut-outs (1), more precisely, the radius of curvature (r) of the wedge edge, the wedge angle (α) between the wedge surfaces of the cut-outs and the base side (b) of the wedge-shaped cut-out.

Figure 3a shows a plate-shaped first body (6) having a plurality of capillaries (7). Figure 3b shows a second body in the form of a base plate (8) having two columnar projections (9) and (10). The projection (9) carries three wedge-shaped cut-outs (1) in its cylinder surface, and the protection (10) carries four wedge-shaped cut-outs (1). When the two bodies are placed against one another, the free end of each wedge-shaped cut-out (1) lies against the projections (9) and (10) in the exit area of in each case one of the capillaries (7). The projection (9) is assigned to three capillaries, and the projection (10) is assigned to four capillaries.

The space which is delimited by the upper side of the base plate (8) and the underside of the first body (6) and which is in the vicinity of the projections (9) and (10) is the collecting chamber, which is adjacent to the base side of the wedge-shaped cut-outs.

Figure 4 shows a partial view of the underside of a first body (6) with the exit ends of three approximately circular capillaries (12). The columnar protection (11) shown in cross section has three wedge-shaped cut-outs (1), each of which is assigned to a capillary. The free end of the wedge edge of each wedge-shaped cut-out (1) is within the exit area of in each case one capillary (12).

Figure 5 in combination with Figure 2 shows a one-piece design in which the region of transition from a capillary into a relatively large collecting chamber is shown in inclined view as a cut-off section. The capillary (14), the wedge-shaped cut-out (13) and the collecting chamber (15) having a rectangular cross section are arranged in a one-piece body (16). The wedge-shaped cut-out (13) is seamlessly adjacent to the exit end of the capillary (14) having a rectangular cross section. The wedge edge of the wedge-shaped cut-out (13) is perpendicular to the wall of the capillary (14) and extends down to the base surface of the collecting

chamber (15). In the design shown in Figure 5, a cover plate (not represented) is, if desired, present on the upper side of the one-piece body (16).

Figure 6 shows a further form of a one-piece design in inclined view. The capillary (14), the wedge-shaped cut-out (17) and the collecting chamber (15) having a circular cross section are arranged in a one-piece body (16). The wedge-shaped cut-out (17) is seamlessly adjacent to the exit end of the capillary (14) having a rectangular cross section. The wedge edge of the wedge-shaped cut-outs(17) is inclined with respect to the wall of the capillary (14) and hits the wall of the collecting chamber (15) above the base of this collecting chamber. In the design shown in Figure 6, a cover plate (not represented) may be present on the upper side of the one-piece body (16).

Figure 7a shows a plate (20) on one side of which three devices according to the invention are shown. A plurality of columnar projections (22) and a plurality of projections (23) in the form of cross pieces are provided on the base (21) of the first collecting chamber. Each of the columnar projections, one of which is shown enlarged in Figure 7d, is provided with three wedge-shaped cut-outs (24). Each of the projections in the form of cross pieces, one of which is shown enlarged in Figure 7c, is provided with a plurality of wedge-shaped cut-outs (25). The free volume between the columnar projections (22) and the projections (23) in the form of cross pieces forms the volume of the first collecting chamber.

The edge (26) of the base (21) of the first collecting chamber is adjacent to the second collecting chamber with base (27). A plurality of wedge-shaped cut-outs (28), some of which are shown enlarged in Figure 7e, are provided in the step at the end of the first collecting chamber. The cut-outs (28) extend from the base (21) of the first collecting chamber to the base (27) of the second collecting chamber. The free volume above the base (27) forms the volume of the second collecting chamber.

The third collecting chamber in the form of a circular recess with base (29) is provided in the base (27) of the second collecting chamber. The edge (30) of this recess is provided with a plurality of wedge-shaped cut-outs (31), some of which are shown enlarged in Figure 7f. The wedge-shaped cut-outs (31) extend from the base (27) of the second collecting chamber to the

base (29) of the third collecting chamber. The free volume above the base (29) forms the volume of the third collecting chamber.

Figure 7b shows the cover of the collecting chambers. The cover (32) for the first collecting chamber is a separator membrane provided with capillaries whose underside is supported on the ends of the columnar projections (22) and on the longitudinal sides of the projections (23) in the form of cross pieces and on the edge (33). The cover (32) delimits the first collecting chamber to the top. The liquid to be separated is applied to this separator membrane. The cover (34) is a plate whose underside is supported on the edge (35) and which delimits the second and third collecting chambers to the top. A vent opening (36), through which the air from the collecting chambers escapes as soon as the liquid removed from the separator membrane enters the collecting chambers, is provided in the plate (34). The removed liquid is present in a defined layer thickness, as advantageous or necessary, for example, for optical analysis, between the underside of the cover (34) and the base (29) of the third collecting chamber. For optical analyses in transmitted light, the plate (20) consists of transparent material.

Figure 8 shows a cross section through Figure 7a on line A – A, showing the plate (20) with the columnar projections (22) and the base (21) of the first collecting chamber and the base (27) of the second collecting chamber and the base (29) of the third collecting chamber. Wedge-shaped cut-outs (28) are provided at the edge of the second collecting chamber. Wedge-shaped cut-outs (31) are provided at the edge of the third collecting chamber.

The first collecting chamber (37) lies between the projections (22), the base (21) and the underside of the separator membrane (32). The second collecting chamber (38) lies between the base (27) and the underside of the cover (34). The third collecting chamber (39) lies between the base (29) and the underside of the cover (34).

The capillarity of the collecting chambers shown in Figures 7a and 8 is determined by their height (separation between the underside of the cover and the base of the respective collecting chamber). The height of the second collecting chamber (38) is greater than the height of the first collecting chamber (37). The height of the third collecting chamber (39) is greater than

the height of the second collecting chamber.

Figure 7a shows two forms of projections, namely columns (22) and cross pieces (33), in the first collecting chamber. By contrast, it is possible for the first collecting chamber to contain only columnar projections (22) in virtually any desired spatial arrangement or only projections (23) in the form of cross pieces.

The wedge-shaped cut-outs (24; 25; 28; 31) can be directly adjacent to one another in a saw-tooth arrangement, or they can be provided at a separation from one another; both variants are shown in Figures 7a, 7c, 7d, 7e and 7f.

Example 1: Filling of a microchamber

Two circular chambers with a diameter of 1 millimetre and a depth of 500 µm are formed by deep X-ray lithography in a PMMA plate with a thickness of about 1.5 millimetres. A channel which connects the two chambers runs between the two chambers. The channel has a width of 100 µm, a depth of 100 µm and a length of about 5 millimetres. A wedge-shaped cut-out which extends as far as the base of the chamber is provided at the mouth of the channel in one of the two chambers (see Figure 5). The wedge-shaped cut-out has a wedge height of 100 µm, its base side has a length of 50 µm, and the radius of curvature of the wedge edge is 1 µm.

No wedge-shaped cut-out is provided at the mouth of the channel in the other chamber.

If the channel between the two chambers is filled with a drop of a liquid, for example ink, this liquid only runs into the chamber in which a wedge-shaped cut-out is provided at the mouth of the channel. The other chamber, in which no wedge-shaped cut-out is provided at the mouth of the channel, remains unwetted.

Example 2: Device for separating blood plasma from whole blood

A glass-fibre/cellulose membrane is laid on a PMMA plate with a thickness of about 1.5 millimetres which has been produced by injection moulding. The plate is provided with cross pieces on its upper side (see Figure 1c). The cross pieces have a width of 500 µm and a height of 120 µm and have a separation of 400 µm from one another. Wedge-shaped cut-outs which

extend 300 µm into the cross piece and have a wedge angle of 25 degrees are provided on a longitudinal side of each cross piece. The radius of curvature of the wedge edge is 2 µm. The separation of the cut-outs from one another is 600 µm. A channel with a width of 400 µm and a depth of 120 µm is located between each two cross pieces between the underside of the membrane and the upper side of the plate. All channels taken together form the collecting chamber. The volume of the collecting chamber is 5.4 microlitres per square centimetre of plate area.

If whole blood is dribbled onto the membrane, the blood cells are separated from the blood plasma in the membrane. By means of the wedge-shaped cut-outs at the sides of the cross pieces, the blood plasma is transported out of the membrane into the collecting chamber, where it is collected. The blood plasma remains in unchanged form, i.e. it is not mixed with another liquid, and can be used directly for subsequent analysis.

CLAIMS:

1. A device for removing a liquid from at least one capillary into a collecting chamber comprising:

a structure that defines a capillary passage having an exit end, and a wedge-shaped cut-out at said exit end;

said wedge-shaped cut-out having:

a root formed by a wedge edge that defines a radius of curvature which is smaller than half the smallest dimension of said capillary passage, and a wedge angle between wedge surfaces of the cut-out of less than 150 degrees; and

a collecting chamber adjacent to a lower end of the wedge-shaped cut-out.

2. A device according to Claim 1, wherein said wedge angle is less than 90 degrees.

3. A device according to Claim 1 or Claim 2, wherein said structure is of two-piece design for removing a liquid comprising a first wedge through which said capillary passage extends, and a second body which has a collecting chamber which is provided in a second body where

said wedge-shaped cut-out provided in at least one projection located on a base plate as the second body, said projection having a free end that is in contact with a surface of said first body wherein in which the exit end of said capillary passage is located; an entry end of the wedge-shaped

cut-out lying within the area of said exit end of said capillary passage.

4. A device according to Claim 3, where said first body includes:

a single capillary passage therein;

or a plurality of discrete capillary passages or discrete gaps;

or includes multiple capillary passages in the form of pores or gaps therein where the first body is:

an open-pore membrane,

or an open-pore sintered body,

or a nonwoven, felt or paper.

5. A device according to Claim 3 or Claim 4, wherein the wedge-shaped cut-out has a wedge-edge that extends perpendicular to said surface of the first body in which the exit end of the capillary is located, or is inclined to this surface by an angle of at least 20 degrees.

6. A device according to any one of Claims 3 to 5, wherein said at least one projection has the shape of a column, a cone, a pyramid, or a cross piece.

7. A device according to Claim 1 or Claim 2 of one-piece design wherein in each case a single wedge-shaped cut-out runs seamlessly into the at least one capillary at its exit end.

8. A device according to Claim 7, wherein said wedge-shaped cut-out is provided in a wall of said collecting chamber into which said at least one capillary passage opens, the existing end of said wedge-shaped cut-out being located in the wall of said capillary passage in the vicinity of the exit end thereof.

9. A device according to Claims 7 and 8, wherein said wedge-shaped cut-out has a wedge edge that extends perpendicular to the wall of said capillary passage, or that is inclined to the wall of the capillary passage by an angle of at least 20 degrees.

10. A device according to any one of Claims 1 to 9, including a plurality of groups each group which comprises at least one wedge-shaped cut-out and a collecting chamber are arranged one after the other, a dimension determining the capillarity of the respective collecting chamber being greater than the capillarity-determining dimension of the respective collecting chamber arranged therebefore.

11. Use of a device according to any one of Claims 1 to 10 for separating a liquid from a liquid medium.

12. Use of a device according to any one of Claims 1 to 11:

for separating a liquid from a solid-containing medium by means of a filter membrane;

or for separating blood plasma from whole blood by means of a separator membrane,

or for filling a well of a microtitre plate from a feed capillary.

FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS

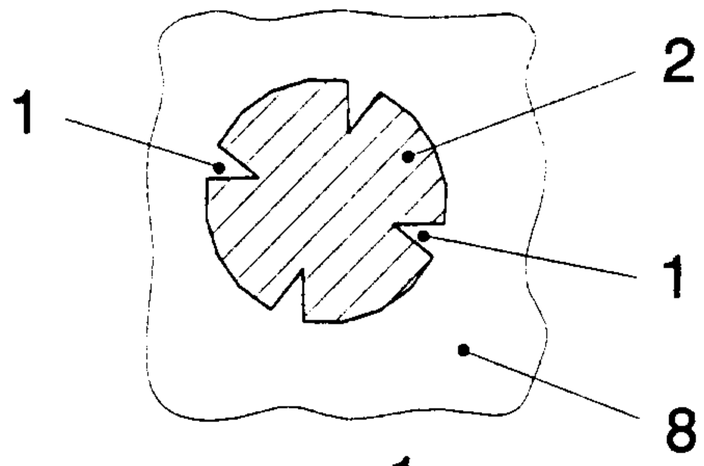

Fig. 1a

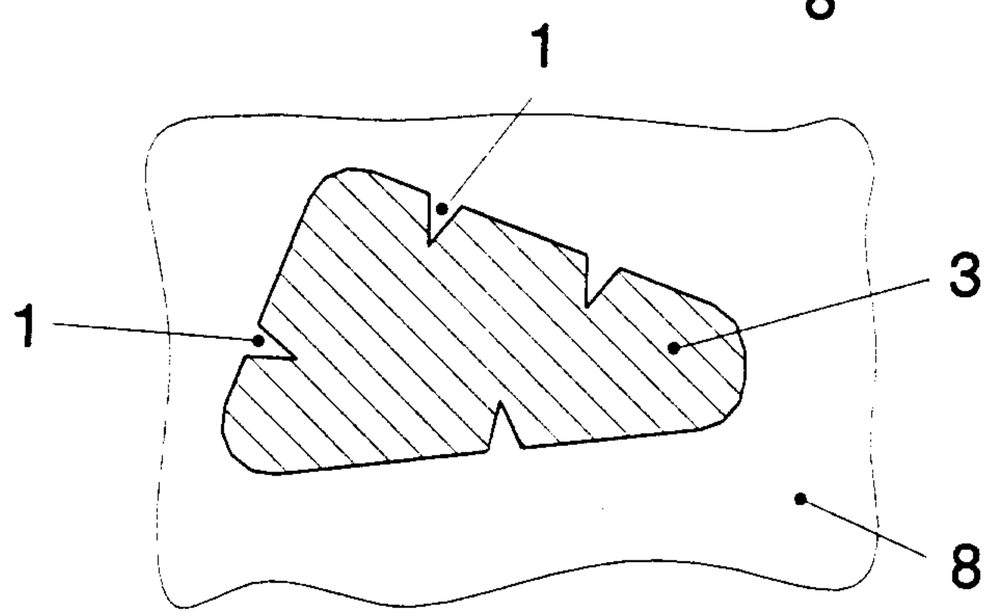

Fig. 1b

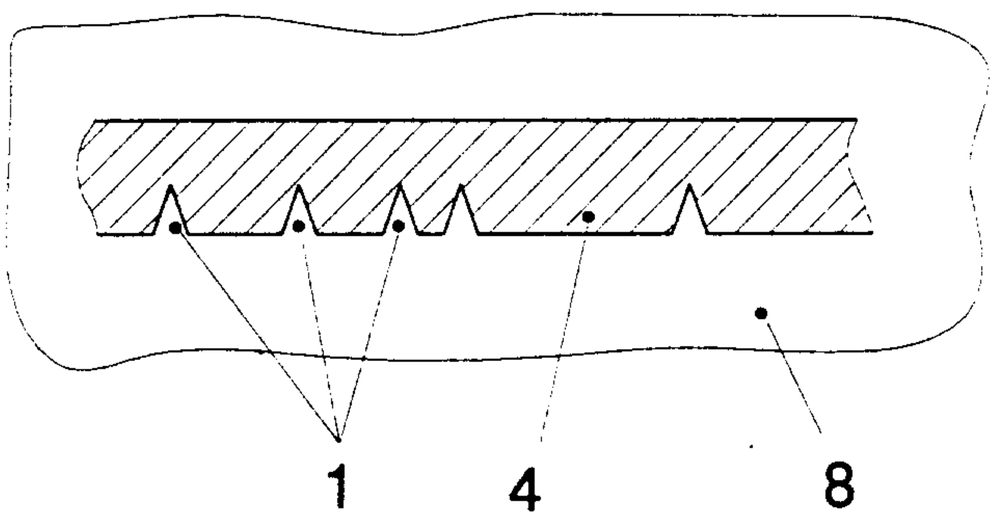

Fig. 1c

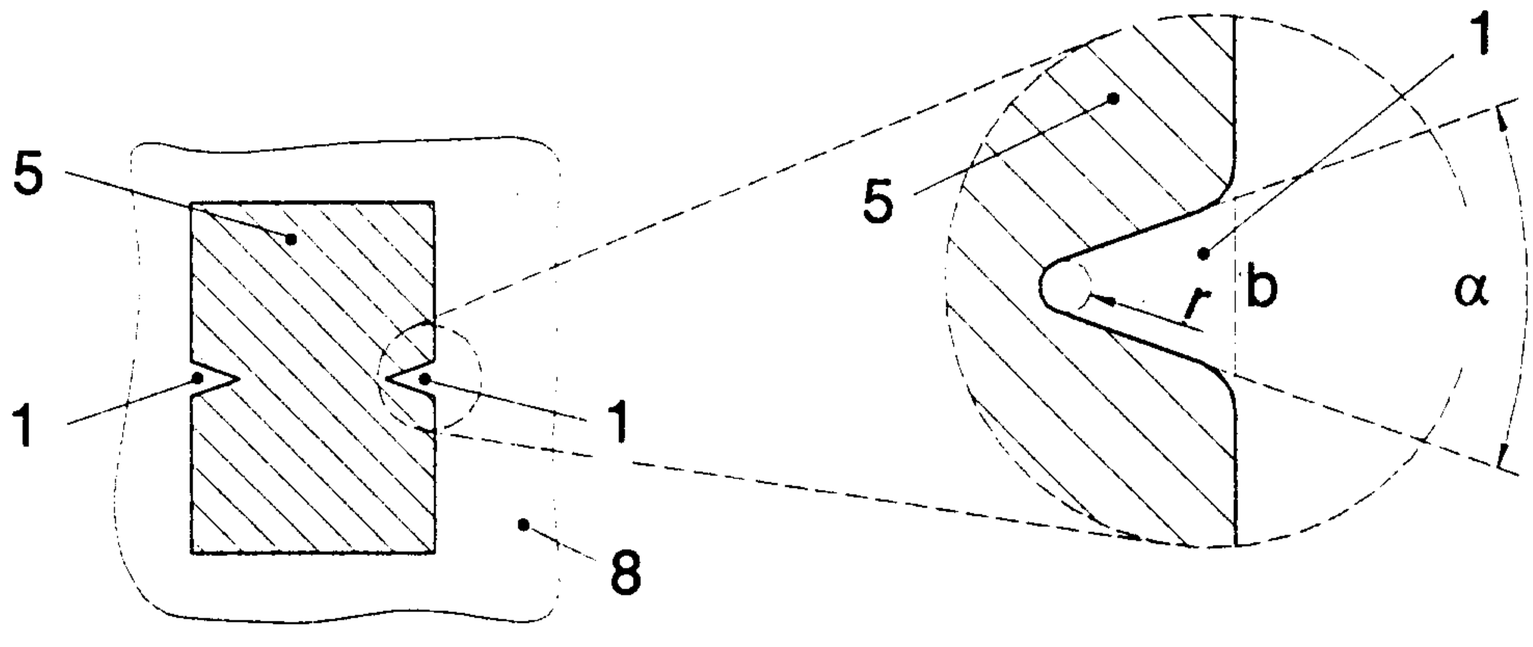

Fig. 2a

Fig. 2b

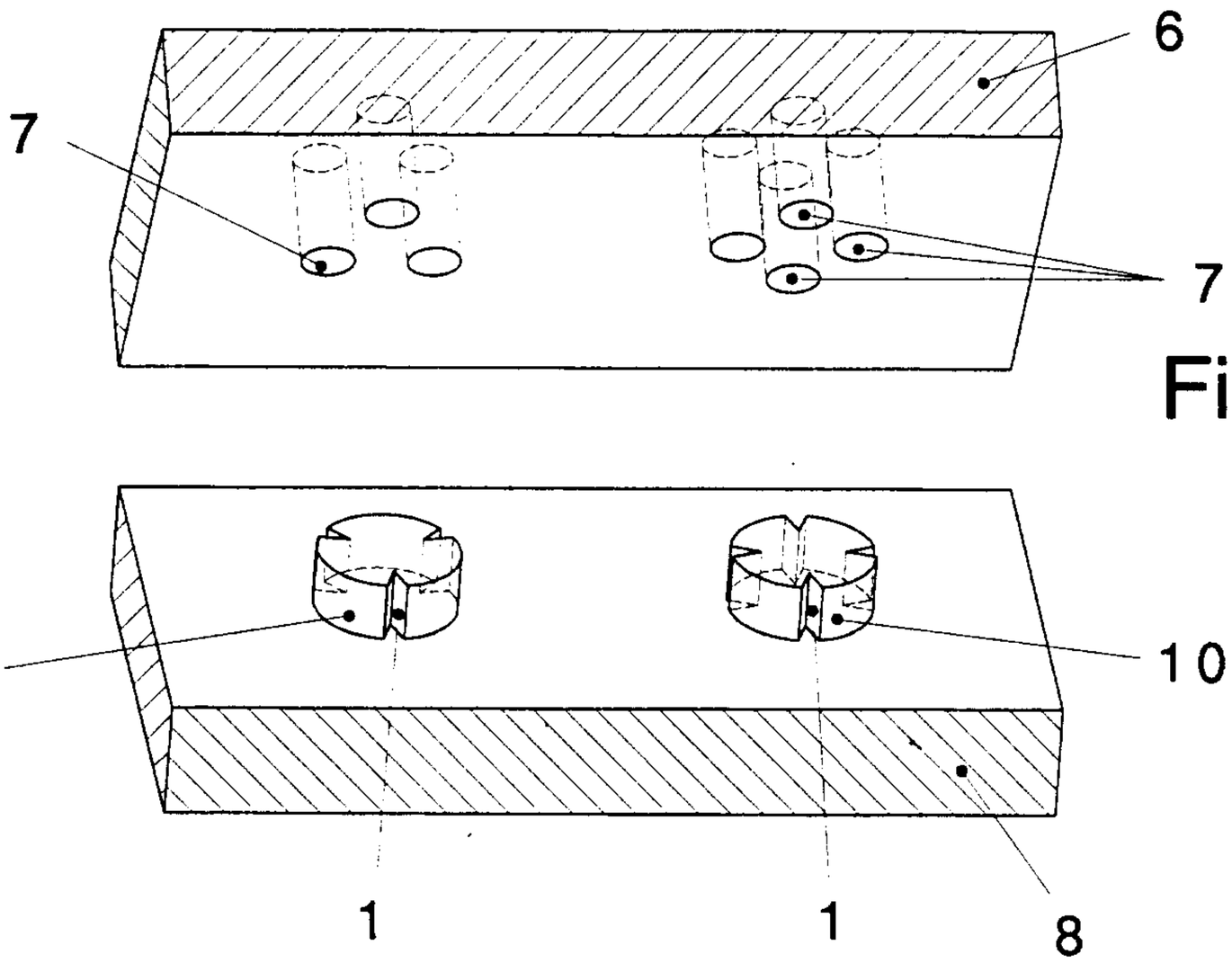

Fig. 3a

Fig. 3b

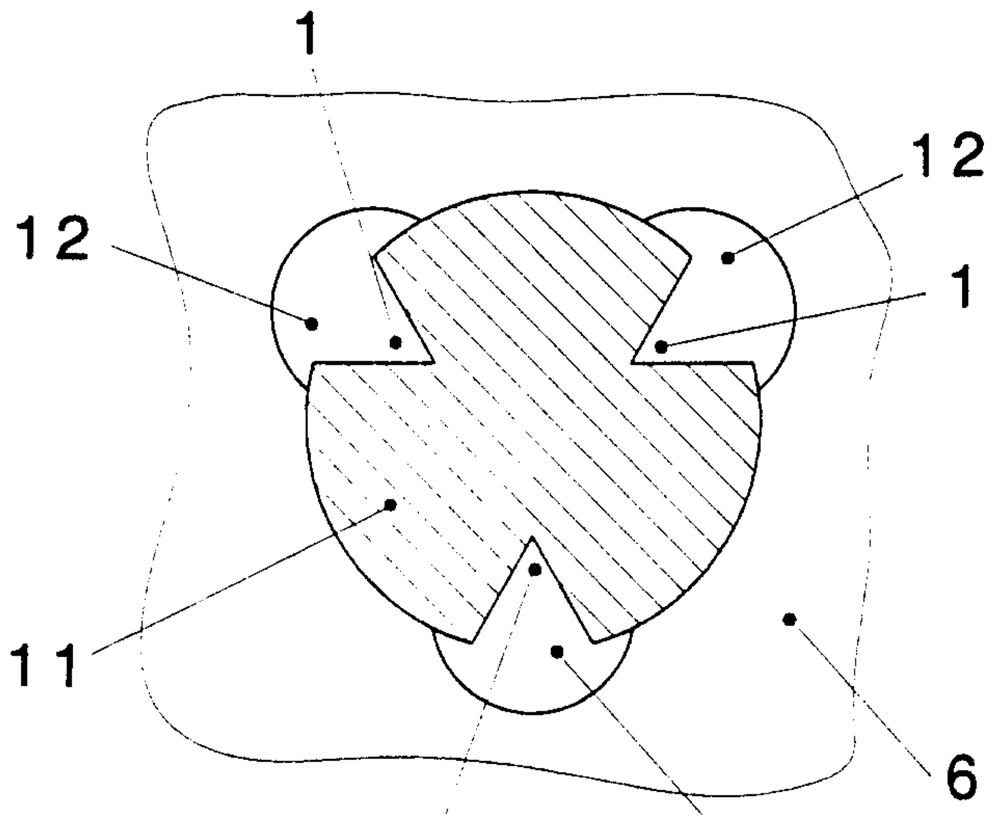

Fig. 4

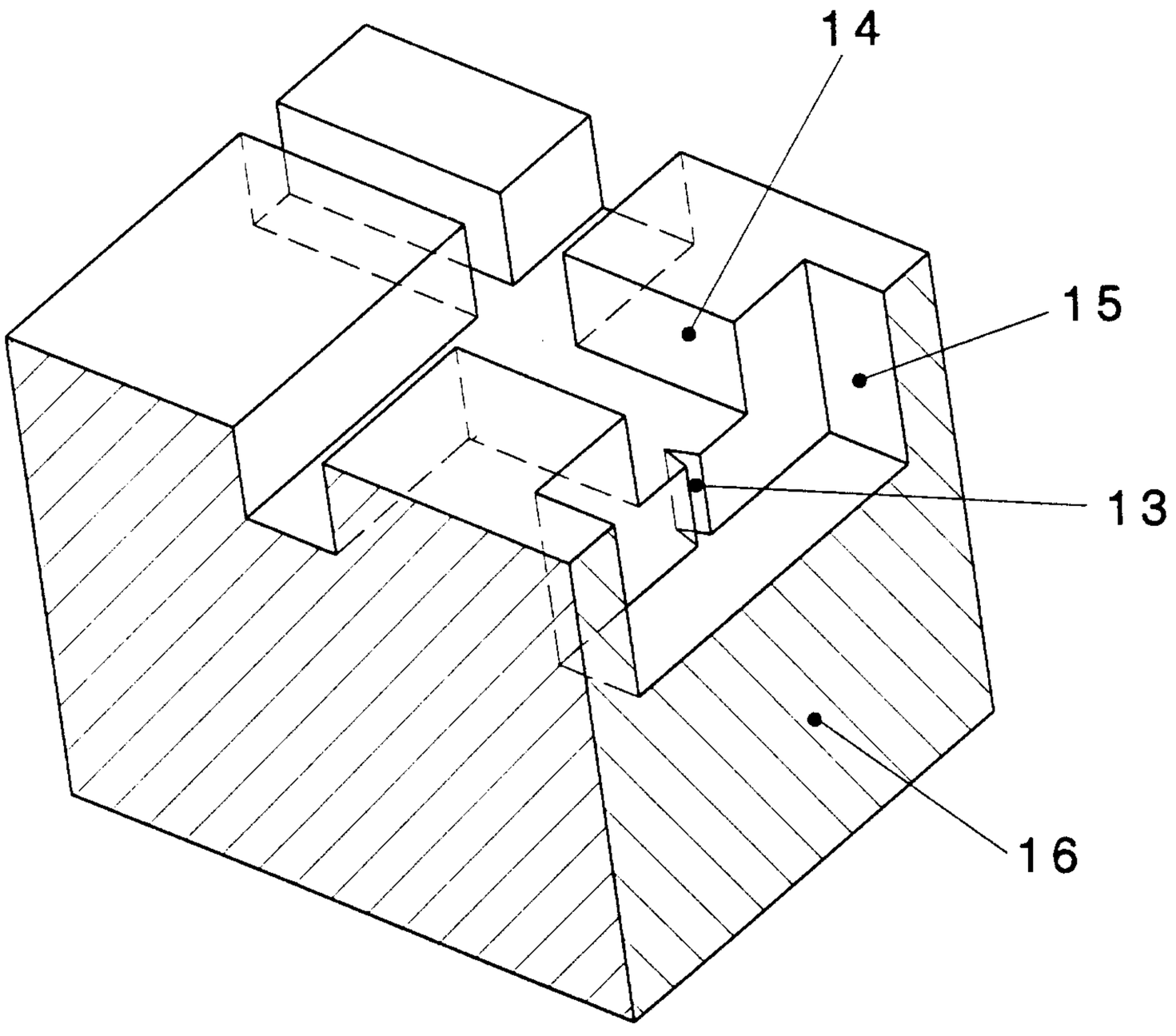

Fig. 5

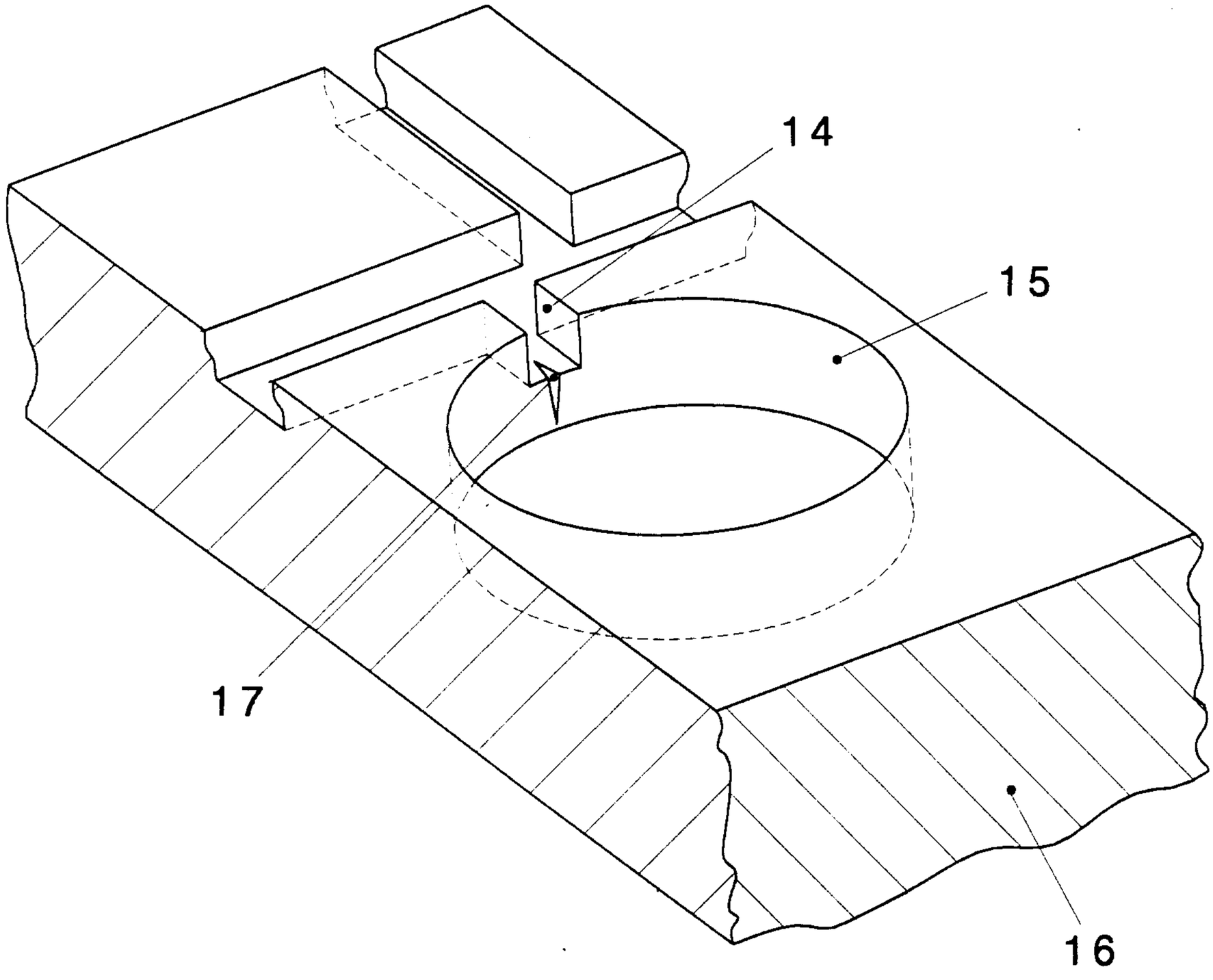

Fig. 6

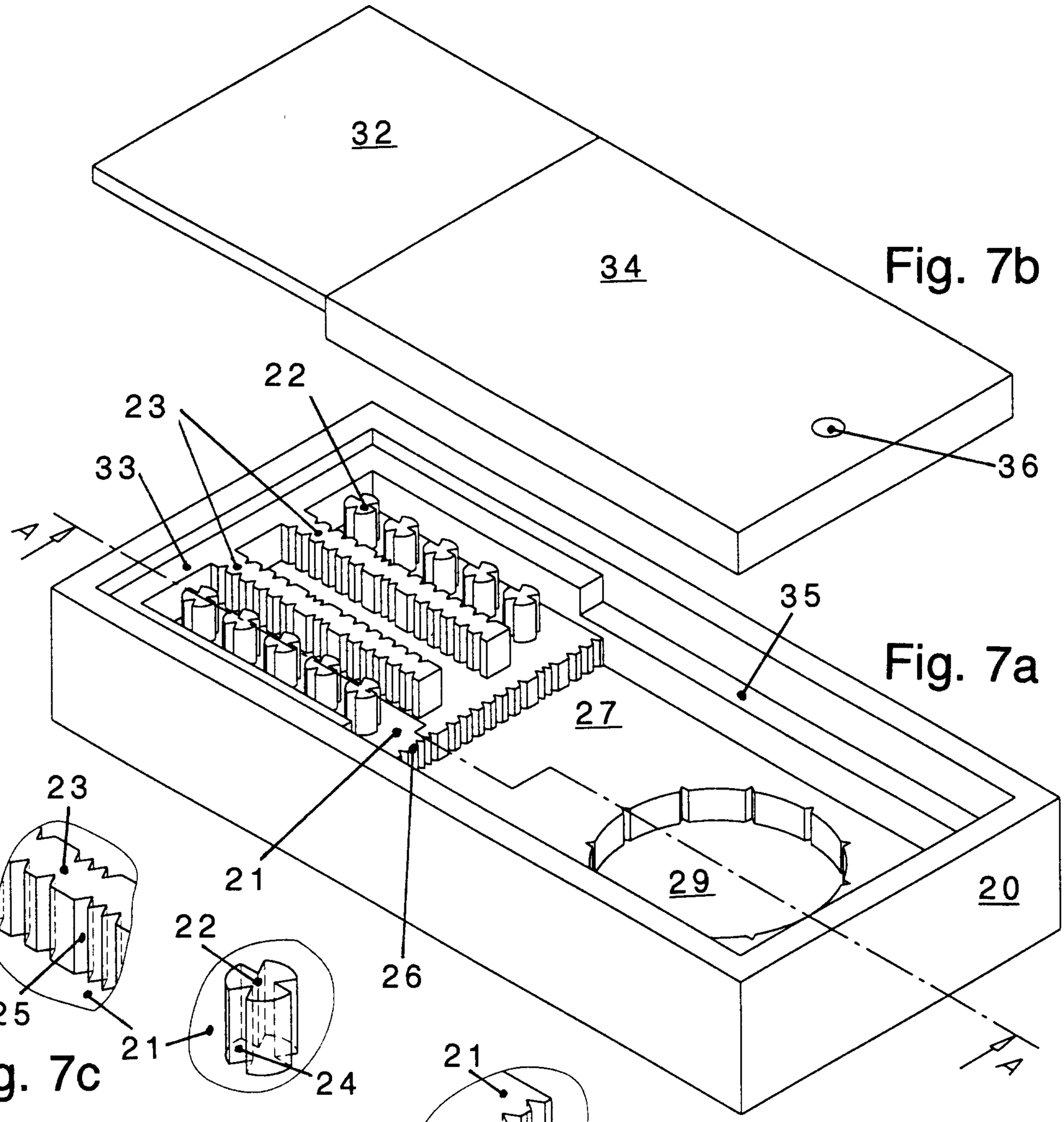

Fig. 7a

Fig. 7c

Fig. 7d

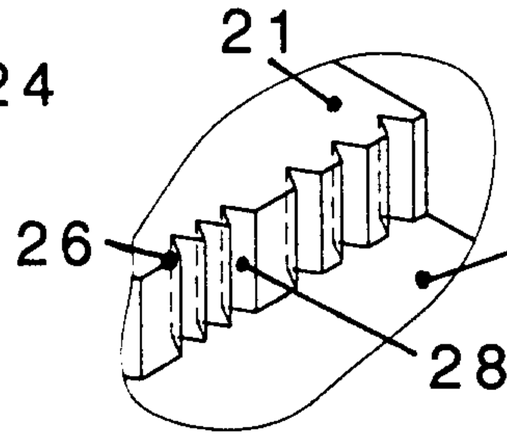

Fig. 7e

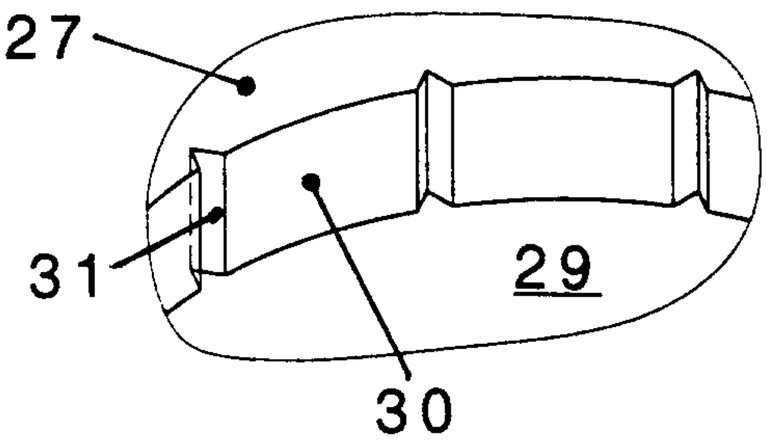

Fig. 7f

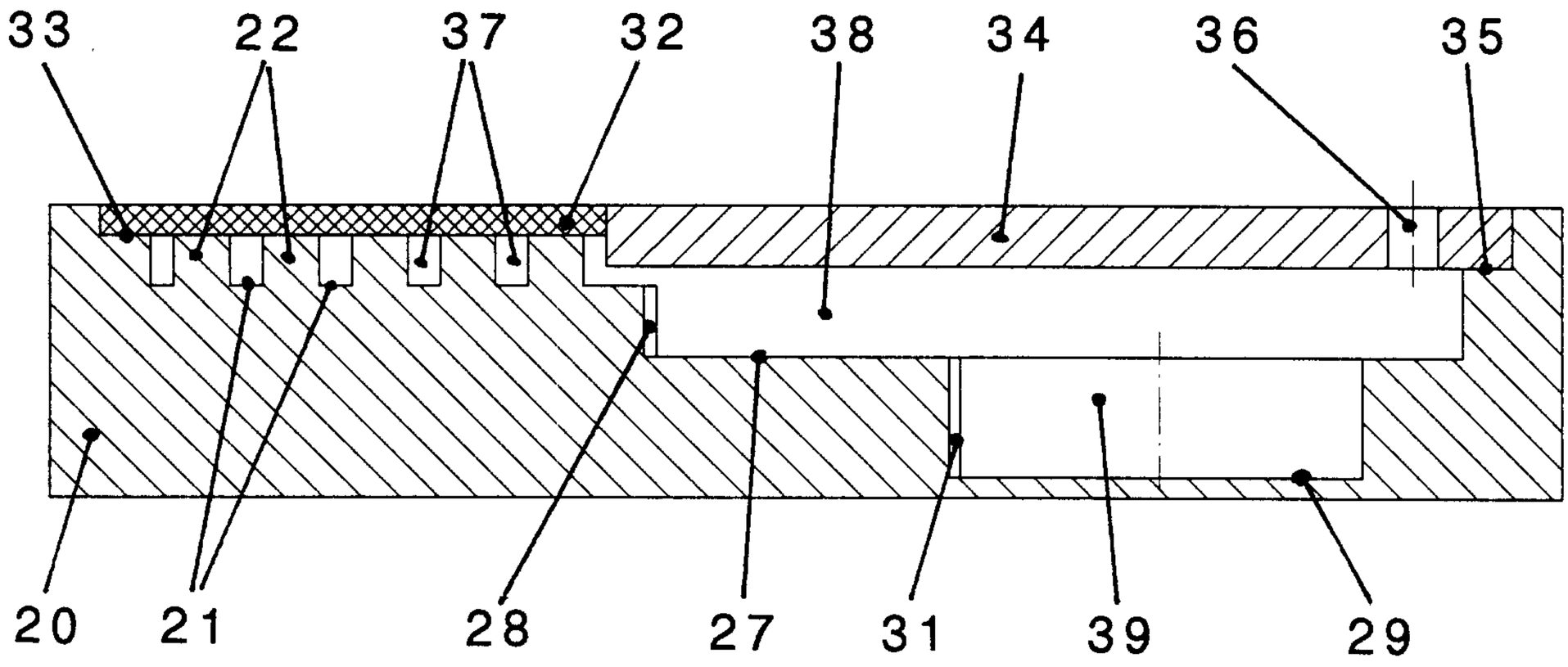

Fig. 8