(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100263 A1

(51) International Patent Classification[7]: A61B 5/00, 17/34

(21) International Application Number: PCT/GB02/02632

(22) International Filing Date: 12 June 2002 (12.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0114290.0 12 June 2001 (12.06.2001) GB

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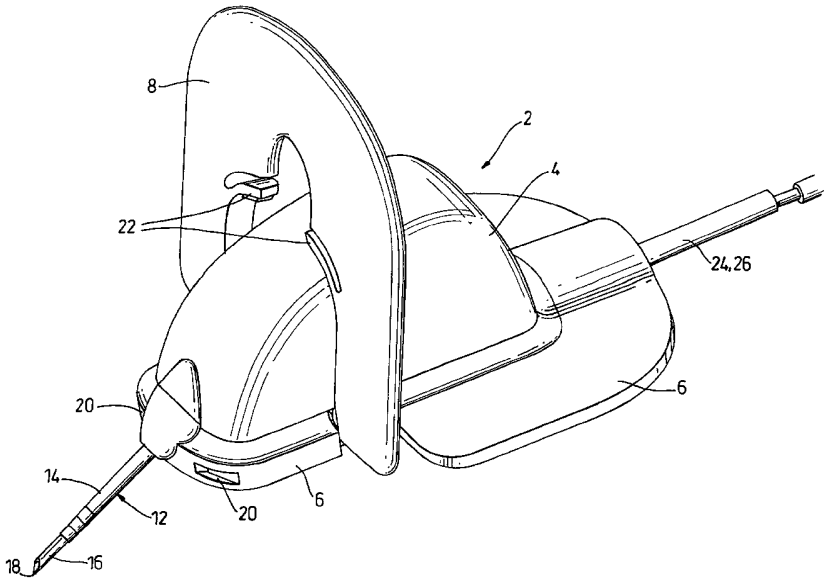
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Continued on next page]

(54) Title: ANALYTICAL DEVICES HAVING THE SENSOR WITHIN THE TROCAR



(57) Abstract: Devices, kits and methods are disclosed that employ a electrode for insertion into a patient in which a flow of liquid is supplied to the sensing surface of the electrode to keep away undesirable contaminants or fouling components, while allowing the desired analyse to diffuse towards the electrode and thus be determined. The invention is particularly concerned with a device which enables the electrode to be correctly inserted at a site in a patient's body, e.g. in the interstitial space between the skin and vascularised tissue below, and in a way that is acceptable to the patient and which does not damage the electrode and with a fluid priming and delivery system for supplying the a microflow fluid to the inserted electrode.

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Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

ANALYTICAL DEVICE HAVING THE SENSOR WITHIN THE TROCAR

Field of Invention

The present invention relates to analytical devices and kits, to methods of using them to determine analyte concentrations, and in particular to devices and kits comprising electrodes for monitoring analyte concentrations in vivo.

Background of Invention

It is well known to use electrodes as sensors in systems and apparatus for measuring a variety of parameters by electrochemical analytical methods. Increasingly, these techniques have been used to the study of analyte concentrations in tissues, and especially living tissue, as it offers the potential of monitoring rapidly changing parameters in real time, providing both an indication of the actual amount of analyte present in the tissue and whether that amount is changing, thereby helping to avoid delays caused by taking samples and analysing them using traditional techniques in a laboratory.

However, there are many problems that need to be addressed in order to realise the advantages. Some of these problems arise from difficulties in quickly stabilising electrodes in vivo so that the readings from them reflect changes in analyte concentration and are not just the result of equilibration with the environment around the electrode or from contamination of the electrode from the surrounding media. There are also problems in keeping a sensing electrode functioning correctly in an in vivo environment where it is prone to fouling with interfering contaminants from the tissue surrounding the insertion site.

Further, there is a need to design electrode sensors that are easy for patients and physicians to use, and work reliably in a clinical setting. It would be a particular benefit to provide a device that embodies these advantages and can be manufactured cheaply enough to be disposable.

PCT/GB93/00163 discloses a method of installing an electrode in place in vivo which comprises the step of providing at the site of insertion a protecting medium which, without injuring the biological environment, suppresses the adverse depressive effect of the electrode's output induced by the biological environment. The protecting medium is then modified or replaced by an aqueous surrounding medium which allows the electrode to become exposed to the surrounding environment, and so allowing the measurement of analytes from the environment. These ideas are further refined in PCT/GB00/03253, an electrode device is disclosed in which a continuous flow of liquid is provided over the surface of the electrode at a sufficiently low rate such that it allows analyte to diffuse from the surrounding environment to the electrode, while inhibiting the flow of contaminants to the electrode surface. Thus, this 'microflow' of the liquid provides a permeable layer flowing over the sensing surface of the electrode at a rate such that the analyte is able to diffuse towards the electrode at a faster rate than the microflow of liquid carries it away.

Summary of the Invention

Broadly, the present invention relates to devices, kits and methods for determining the presence or concentration

of one or more analytes present in a patient, and more especially to providing microflow electrode devices which can be used by patients and physicians. The present invention further relates to providing disposable electrode devices. The present invention is particularly concerned with devices for determining of blood glucose levels to assist in the management of diabetes.

In preferred embodiments of the invention, the devices, kits and methods described below employ the microflow conditions disclosed in PCT/GB00/03253, that is where a flow of liquid is supplied to the sensing surface of the electrode which is sufficient to keep undesirable contaminants or fouling components away from the electrode surface, while still allowing the desired analyte to diffuse towards the electrode and thus be determined. The flow of fluid to the tissue or other medium under examination should be in a quantity low enough to avoid any unacceptable degree of dilution of the tissue or media being monitored at a rate such that the fluid can mingle with the tissue or media and form a zone in which the rate of diffusion at which the analyte can reach the sensing surface of the electrode is greater than the rate of flow of the microflow fluid outwards from the surface.

In one aspect, the present invention concerns an electrode device which enables an electrode to be inserted at a site in a patient's body, e.g. in the interstitial space between the skin and vascularised tissue below, and in a way that is acceptable to the patient and which does not damage the electrode.

In this aspect, the present invention provides an

electrode device comprising:

an electrode assembly for insertion into a patient, the electrode assembly comprising an electrode having a sensing surface, a cannula for supplying fluid over the sensing surface and a trocar for enabling insertion of the electrode assembly, wherein the electrode is retained within the trocar and the trocar is moveable between an extended position and a retracted position such that in the retracted position, the sensing surface of the electrode extends beyond the trocar;

a body portion in which the electrode assembly is mounted, the body portion including a trocar retraction mechanism operable by a user of the device to cause withdrawal of the trocar to the retracted position when the electrode assembly has been inserted in the patient.

Thus, the benefits of this trocar retraction mechanism are (i) that it ensures the sensor tip is delivered reproducibly and accurately to the interstitial tissue to the desired projection beyond the end of the microflow cannula to benefit from the protective microflow effect, (ii) that it prevents accidental damage to the sensor tip upon insertion, since no positive force is required to place the sensor beyond the cannula and (iii) that it keeps the sharp within the body of the device thus avoiding sharp disposal.

Thus, in this aspect, the present invention provide an electrode device in which the trocar is initially fixed in an extended position for guiding the insertion of the electrode assembly at the correct angle and depth into the patient, and subsequently allows the controlled withdrawal of the trocar once correct placement of the electrode has been achieved.

In a preferred embodiment, the cannula, trocar and electrode are arranged concentrically, and more preferably with the cannula outermost and the electrode innermost. In use, this allows the insertion of the electrode assembly into the patient, after which the trocar can be retracted into the cannula to reveal the sensing surface of the electrode. However, other arrangements of the components of the electrode assembly are possible, for example in which the cannula for supplying fluid across the sensing surface of the electrode is separate from the trocar and electrode.

Preferably, the trocar retraction mechanism comprises a retraction arm attached to the body of the device which is moveable to cause retraction of the trocar. In preferred embodiment, the body portion of the electrode device is provided with a base plate for seating the device against the patient and the retraction arm is pivotally attached to the body of the device. The retraction arm is moveable from a first position in which the trocar is extended to a second position in which the trocar is retracted and retraction arm is approximately coplanar with the base plate. This arrangement helps to stabilise the electrode device when it is in place on the patient, assisted by providing the base plate, and optionally the retraction arm, with adhesive pad(s). In a particularly preferred arrangement for locating the electrode in the interstitial space under the skin of a patient, the electrode assembly including the trocar is fixed at an angle of between 20° and 40°, and more preferably about 30° to the base plate and the trocar extends beyond the base plate to provide an insertion depth of about 5 mm. The electrode can be inserted into the patient by sliding the base plate along the surface

of their skin in the direction of the trocar so that it inserts into the interstitial space.

In a preferred embodiment, the end of the trocar which is positioned within the body of the device is linked via a retraction cord to the retraction arm so that movement of the arm pulls on the cord and hence retracts the trocar.

The retraction mechanism may advantageously further include securing means to ensure that the retraction of the trocar into the device is one way, i.e. to avoid the sharp end of the trocar becoming exposed to patient or physician after the device has been used. This can be achieved by including a ratchet formed by opposing teeth associated with the trocar and the retraction mechanism so that withdrawal of the trocar causes the teeth to slide past each other and lock the retracted trocar in place.

In a preferred embodiment, the present invention further provides a locking mechanism to prevent premature retraction of the trocar prior to insertion into the medium/patient. If this happened, then the electrode would become exposed, risking damage to the electrode and especially its sensing surface, and damage to the patient, if an attempt was made to insert the exposed electrode into tissue. The locking mechanism can take the form of a locking pin which fixes the retraction arm in place until the locking pin is removed.

The electrode device preferably includes a control and read out device for making determinations of analyte concentration using the electrode and displaying the results to users of the device. The control device can

be connected to the electrode via an electrical connector.

The electrode may be any of the forms of electrode known in the art, and is preferably a bare electrode, usually formed of a metal or combination of metals such as platinum, platinum-iridium, gold or silver. The electrode, and more particularly the sensing surface of the electrode can be covered with a membrane, coating or other barrier which is selectively permeable to analyte while inhibiting fouling of the electrode surface, e.g. as caused by its environment or otherwise improve its performance. Examples of permeable or protective coatings include electrolytically oxidised polyphenol diseribed in EP 0 672 167 A or phenolic compound/surface active agent coatings described in PCT/GB00/03108. Examples of protective membranes are disclosed in PCT/GB00/02665 (compositions comprising an impermeable polymer and a polyvinylpyridine) and WO99/10520 (polyurethane modified by surfactant). Preferred electrodes of the invention have sensing surface which include immobilised enzyme, e.g. immobilised on the surface of the electrode or in one or more fenestrations along its sensing surface (e.g. see PCT/GB00/03054).

The analyte determined using the electrode is preferably an analyte that is capable of oxidation by an oxidase type enzyme. Thus, the electrode device can be used to determine the presence, concentration or change in concentration of the analyte. A preferred analyte is glucose which can be detected using immobilised glucose oxidase.

The electrode device preferably uses an electrolytic mode

of analysis, and more preferably an amperometric mode of analysis. Examples of suitable types of electrode include:

(a) any of the metals in the form of the element or a compound used for the study of electrochemically active species (ascorbate, paracetamol etc), membrane covered electrodes using such metals and membranes of materials such as ion-exchange polymers or materials of controlled porosity. These include materials such as polyether sulphones (PES), polyvinyl chlorides (PVC) and products such as Nafion; these can be used in conjunction with neurotransmitters such as dopamine and noradrenalin.

(b) oxidase based enzymes electrodes for which the relevant oxidisable species may be glucose, lactate etc, for which the appropriately matched enzyme system can be used.

(c) dehydrogenase based enzyme electrodes in which the fluid supplied to the electrode contains the co-factor required to facilitate functioning of the electrode.

(d) oxygen electrodes, which are similar to enzyme electrodes but can be operated at higher voltages, e.g. approximately +0.6V against a silver/silver chloride electrode (Ag/AgCl) reference electrode.

In a particularly preferred embodiment, the electrode, preferably concentric in nature formed using platinum/iridium or platinum within a stainless steel cannula, has a protrusion of platinum/iridium about 0.5 mm beyond the end of the steel cannula. The active sensor tip (the Pt/Ir) is coated sequentially using preferably an interferent rejection layer; an enzyme layer; outer diffusion limiting/biocompatible layer. In use, the sensor is held within a cannula that is inserted

subcutaneously to a depth of preferably 5mm below the skin surface at an insertion angle between about 20° and 40°, and most preferably about 30°. Microflow fluid, preferably Ringer's solution, possibly including isotonic saline, isotonic saline including 5mM potassium or phosphate buffered saline, is initially perfused actively across the sensor tip under an initial priming force applied by the fluid retaining pouch. The act of this priming force is to (i) expel any air from the device prior to insertion (ii) to initially hydrate the interstitial tissue around the sensor which allows rapid equilibration of the sensor within the tissue, allowing reliable glucose measurements to be made within 30 min of sensor installation. Following the initial positive pressure applied to the fluid pouch, the negative interstitial tissue pressure naturally draws microflow fluid at a rate typically in the range 30-60µl/h.

The electrode device preferably also includes fluid delivery device for supplying fluid to the cannula, e.g. so that a microflow of fluid can be established over the sensing surface of the electrode in use. The fluid delivery device may comprise a tube linked to an external supply of fluid or the fluid may be supplied from a reservoir inside the body portion of the device.

Preferably, the device includes in the flow path from the fluid delivery device to the cannula, a chamber or length of tubing between the fluid connection and the cannula through which fluid is supplied. This has the advantage of helping the fluid supplied through the cannula to equilibrate to body temperature prior to infusion into the patient. This assists patient compliance and also helps to minimise errors that may be caused by

differences in the temperature of the microflow fluid.

In a further aspect, the present invention provides a fluid delivery device for supplying fluid to an electrode device, the fluid supply device comprising:

a fluid supply bag containing fluid and having a port; and,

a casing adapted to receive the fluid supply bag, the casing including one or more formations adapted to exert pressure on the fluid in the bag to cause an initial supply of fluid to remove air from the electrode device and to provide fluid at the site of insertion of the electrode, and thereafter to supply fluid at a lower flow rate.

Thus, in this aspect of the invention, the fluid delivery device primes the electrode device by expelling air from the fluid connector and the electrode assembly, and supplies an initial volume of fluid around the sensing surface of the electrode which has the advantage of reducing the time before measurements can be made. After the initial higher flow rate of fluid, the device then supplies a lower flow rate (e.g. at a microflow rate), assisted by a slight negative tissue pressure where the electrode is implanted into a patient.

The formations can be one or more ridges or protrusions or a spring formation provided on the inside of the casing.

The priming procedure can be facilitated by providing a fluid pathway between the trocar tip and the cannula through which air or microflow fluid can be expelled on priming. The fluid pathway may be provided by provding

the trocar tip with a flattened region (as shown in Figure 10), an aperture or other formation to provide the necessary route for the expulsion of air or fluid.

In a preferred embodiment, fluid is supplied to the electrode device via the tube from a separate fluid supply bag. The fluid supply bag can be housed in a casing and comprises a port for connection to the tube. Conveniently, one of the port and the end of the tube can be provided with a self sealing membrane and the other with a spike, allowing the two to be joined together in an airtight and sterile manner. Alternative constructions such as male and female connectors will be apparent to the skilled person.

The fluid supplied to the electrode can in addition to providing the microflow semi-permeable layer over the sensing surface of the electrode can include one or more ingredient required for the reactions taking place at the electrode or to improve the performance of the electrode or device. These ingredients can include anti-coagulants for inhibiting coagulation on the electrode surface, such as heparin, hirudine, prostaglandin, a carboxylated amine such as EDTA; substances for modifying the viscosity of the fluid; an analgesic; one or more components of a buffering system; isotonicising agents; anti-inflammatory agents; preservatives; sterilising agents; agents to render tissues more permeable to liquids or electrolytes; or antibiotics.

In a further aspect, the present invention provides an electrode device and a fluid delivery device as described herein.

In a further aspect, the analyte determinations made using the electrode device are used to control the administration of a pharmacologically active agent to a patient. In this aspect, the present invention provides an electrode device as described herein in combination with a drug delivery device, the drug delivery device comprising a controller for receiving analyte concentration data from the electrode device and a drug reservoir for providing doses of drug to the patient operable under instructions from the controller. Thus, in this aspect, the present invention allows continuous real time monitoring of an analyte concentration and consequent dosing with the drug in response to the concentration of the analyte. This aspect of the invention is particularly suited to the treatment of diabetes with insulin or an anti-diabetic drug, controlling the administration of the drug by determining glucose concentrations (e.g. measurements made interstitially), as it reduces the fluctuations in glucose and insulin levels that result from conventional intermittent measurement and treatment.

In a further aspect, the present invention provides a method of determining an analyte in vivo in a patient, the method comprising:

connecting the electrode device to a fluid supply device, the devices being as described above;

priming the electrode device by introducing fluid from the fluid delivery device to flush air from the electrode device;

locating an electrode device on the patient and inserting the electrode assembly;

retracting the trocar using the trocar retraction mechanism to expose the electrode;

supplying fluid through the cannula to flow over the electrode surface; and,

making one or more measurements of analyte concentration using the device

The method may involve the optional step of securing the device in place using an adhesive pad present on the device or an adhesive pad placed over it.

The method may involve the further step of dosing the patient with a drug in response to the determination of analyte concentration.

Embodiments of the present invention will now be described by way of example and not limitation with reference to the accompanying figures.

Brief Description of the Figures

Figure 1 shows an external, perspective view of the electrode device ready to use with the locking pin removed.

Figure 2 shows an external, perspective view of the electrode device with the locking pin in place.

Figures 3 and 4 show internal views of the electrode device, in particular showing the support for the electrode assembly and the trocar retraction mechanism.

Figure 5 shows representation of the locking pin.

Figure 6 shows the electrode sensor, and in particular a preferred geometry for the sensor.

Figure 7 shows the bag for supplying fluid to the electrode assembly.

Figure 8 shows a housing for the fluid supply bag.

Figure 9 shows a fluid connector for linking the fluid supply bag to the electrode assembly.

Figure 10 shows a preferred form of fenestrated trocar that is designed to allow flow of microflow fluid through the trocar.

In the figures, measurements (where shown) are in millimetres.

Detailed Description

As described above, in one aspect, the present invention relates to a device which facilitates the insertion of an electrode into a patient for making in vivo measurements of analytes, e.g. to determine blood glucose levels to assist in the management of diabetes.

In this aspect, the present invention addresses the problem that electrodes can be sensitive to damage and need to be inserted into a patient's body in a defined manner to provide accurate measurements of analyte concentration. Accordingly, the present invention provides a device which solves the problem of achieving reliable electrode placement, even for an unskilled user, while minimising patient discomfort. In particular, the electrode device can be used to place an electrode in the interstitial space that lies between the skin and vascularised tissue at a depth of a few millimetres.

Figures 1 and 2 show external, perspective views of the electrode device 2. The electrode device 2 comprises a body portion 4, a base plate 6, a retraction arm 8 pivotally attached to the body portion 4 so that it is capable of moving from a first position in which it is approximately perpendicular to the base plate 6 (shown in Figures 1 and 2) to a second position, in which the retraction arm 8 and base plate 6 are approximately coplanar. As shown in Figure 2, the device is provided with a locking pin 10 which prevents movement of the retraction arm 8 before the device is employed. The construction of the locking pin 10 is shown in detail in Figure 5. The locking pin 10 acts upon the trocar retraction arm 8, blocking the movement of the arm in a forwards direction that would otherwise result in the retraction of the trocar 16 into the body of the device under the action of the trocar retraction cord moving over the moulded arc 40. The locking pin 10 blocks movement of 36 by impeding action of 8 on the rounded end of 36 (see Figure 3).

The retraction arm 8 and the body of the device 4 are further provided with cooperating locking formations 20,22 which lock the retraction arm 8 when it has been moved into the second position, thus preventing subsequent movement.

Figures 1 and 2 also show electrical 24 and fluid 26 connectors linking the electrode device to an external display for taking measurements using the implanted electrode and as means for supplying fluid to the electrode assembly 12, described in more detail below. The electrode assembly 12 comprises a cannula 14, containing within it a trocar 16 having a sharp end 18 to

enable the electrode assembly to be inserted into a patient. The electrode itself is held within the cannula and trocar and is disposed so that the sensing end of the electrode extends beyond the end of the cannula 14, i.e. so that cannula, trocar and electrode are arranged in a concentric manner. The electrode is positioned relative to the trocar 16 so that it is held within the trocar 16 in its extended position shown in Figure 1 and 2, but extends beyond the end of the trocar when the trocar is in its retracted position. The end of the electrode assembly can be provided with a removable protective cap (not shown) to cover the sharp trocar prior to use.

Figures 3 and 4 show perspective views of the device in which a housing part of the body portion 4 and retraction arm 8 are removed to show the trocar retraction mechanism inside the device. The electrode assembly is fixed to the base plate 6 via supporting collar 28. The collar 28 supports the electrode assembly 12 at the correct angle for insertion (about 30 degrees) and ensures that the end of the trocar 16 extends beyond the plane of the base plate 6 to allow insertion of the electrode at the correct depth into the relevant tissue. The supporting collar 28 is fixedly joined to arms 30 having inwardly facing teeth 32 which form part of a ratchet mechanism with a second set of teeth 34 provided on retractor cord 36. The retractor cord 36 is linked at a first end to the end of the trocar 16 held within the device 2 and at a second end via a hook formation 42 which is pulled by movement on the retraction arm 8. Between these ends, the retractor cord is supported by formation 38 and runs around a moulded arc 40, and thence connecting to a hook formation 42.

The electrode device 2 is readied for use by removing the cap on the electrode assembly and sliding the base plate 6 along the patient's skin at the site of insertion so that the electrode assembly 12 penetrates the skin to a depth of approximately 5mm, thereby placing the electrode assembly 12 into the interstitial space. After successful sitting of the electrode, the device 2 can be retained in place as the base plate 6 is provided with an adhesive pad on the side adjacent to the patient's skin. Further security can be provided by taping the base plate 6 and/or the retraction arm 8. Once the device 2 is in place, the locking pin 10 can be removed and the retraction arm 8 moved into the second position where it locks in place by the interaction of the cooperating formations 20,22. This movement of the retraction arm 8 causes the retraction cord 36 to be pulled around the moulded arc 40, drawing the trocar 16 up inside the cannula 14 until the teeth 32,34 of the ratchet mechanism pass over each other and lock the trocar 16 in place. This helps to prevent accidental exposure to the sharp trocar after the device has been used as the trocar instead remains locked in the device.

Once the trocar 16 is withdrawn, the electrode is preferably arranged so that it extends beyond the end of the cannula. The inventors found that this improved the presentation of the sensor tip to the tissue in which the measurements are made. In view of this arrangement, the locking pin 10 is useful as it prevents a careless user of the device from prematurely withdrawing the trocar prior to insertion into the patient, causing damage to the electrode and pain to the patient.

The devices of the invention can improve measurements of

analyte by (i) ensuring the sensor tip is presented directly to the tissue without requirement for external pressure to seat the sensor within the cannula, as is the case where the sensor is not incorporated within the device, and/or by (ii) active priming of the device to purge all air pockets which avoid stagnant pools within the device during use. The initial active hydration of the local zone around the sensor tip leads to more rapid equilibration of glucose across the tissue interface, leading to stable/reliable glucose measurements within 30 min of insertion.

The construction of the electrode forms another aspect of the invention. The electrode 42 is shown in Figure 6 and comprises a platinum or platinum iridium core 44 surrounded by a stainless steel sheath 46. The electrode is inserted inside the cannula and trocar as described above and is linked via electrical connector 24 to a conventional control and display device.

The electrode has a sensing tip 48 which can be formed in any of a number of geometries suitable for sensing analytes. In the preferred sensing tip of the electrode shown in Figure 6, the end of the electrode is provided with immobilised enzyme, e.g. glucose oxidase for determining glucose levels in a patient's tissue.

The electrode may be coated with one or more membranes as described above. In a preferred embodiment, the electrode is a platinum-iridium electrode.

Figure 10 shows a preferred form of trocar 16 having fenestrations 17 that are designed to allow flow of microflow fluid through the trocar so that during

priming, air is completely removed from the device, and then during operation, microflow fluid continues to percolate through the cannula 14 and trocar 16 so avoiding any stagnant pools of fluid within the device which could lead to undesirable changes in sensor output that result from leaching of substances from the stagnant areas to the sensor tip.

Also important is the deliberately "flatted" region 15 at the trocar tip, shown in Figure 10. This permits transfer of air/fluid from between the cannula 14 and trocar 16 during priming. Without the micromachined flat, the natural air tight seal between the cannula 14 and trocar 16 could hinder or prevent the expulsion of air from the device during priming, leading to possible complications during insertion.

In further aspects, the present invention concerns the construction of the electrode and the supply of fluid to the sensing tip of the electrode, especially to achieve the microflow conditions as described in our earlier application PCT/GB00/03253. The elements of the fluid delivery system are shown in Figures 7 to 9. A fluid bag 50, typically formed from a flexible plastic material is provided with a port 52 having a tear off cap 54, the port 52 being sealed by a membrane 56. In the preferred embodiment, the fluid bag is about 50 x 80mm in size and holds enough microflow fluid for priming and supplying an electrode device 2 for 24 hours. The fluid bag 50 is adapted to fit inside casing 60. The casing 60 is formed from rigid plastic and comprises two matching halves 62, hinged together and designed to snap in the closed position around the fluid bag 50, with the port of the bag protruding through aperture 64. The casing 60 is

further provided with internal ridges 66, or alternatively a spring formation, to provide a controlled amount of pressure to the fluid bag 50, to pump an initial volume of fluid from the bag for priming the electrode device, principally to flush air from the device before the electrode assembly is inserted into a patient, and to help to control the pressure of the fluid supplied to the electrode after priming to provide fluid to the electrode under microflow conditions. Apertures 68 are provided in the casing to allow it to be carried with a patient, e.g. attaching the casing with a safety pin though the apertures to the patient's clothes.

Figure 9 shows an example of a connector 70 that can be linked to the end of the fluid connector 26. This allows the fluid connector 26 to be linked to the fluid delivery system by removing the tear off cap 54 from the fluid bag inside the casing 60 and pushing the connector 70 through membrane 56 which then seals around the connector 70 providing a robust and sterile seal. As described above, pressure from the casing pumps fluid through the electrical connector 26 and into the cannula 14 of the electrode assembly 12, flushing air from the fluid delivery system and the electrode device 2. The device 2 can then be installed in the patient and the trocar 16 withdrawn to expose the electrode for making measurements of analyte concentration. At this time, the fluid delivery system continues to pump fluid from the fluid bag 50 to hydrate the insertion site so that the electrode can rapidly equilibrate with its surrounding and establish a baseline signal. After this, the fluid delivery system is designed to reduce the flow of fluid, relying on light pressure from the casing and the inherent negative pressure of the patient's body to

provide fluid through the cannula to the vicinity of the electrode.

The electrode assembly 12 is connected via fluid connector 26 to a fluid reservoir 60 which supplies fluid down the space between the electrode and the cannula. In preferred embodiments of the invention, the fluid is supplied under microflow conditions as described in PCT/GB00/03253, i.e. to form a permeable liquid layer of the fluid around the sensing tip of the electrode and maintained over the electrode and interposed between the medium under examination and the active surface of the electrode. The rate of flow of the fluid is controlled so that it allows analyte to pass through permeable liquid layer to the sensing tip by diffusion, while resricting the flow of contaminants from the surrounding medium which can foul the electrode leading to a reduction in its useful working life and/or errors in measurements.

A preferred construction of fluid reservoir 60 and casing are shown in Figure 6.

In order to provide the microflow of fluid, the slight negative pressure of the body of the patient can be employed to help to draw the fluid from the reservoir into the patient's body via the cannula. However, the fluid reservoir shown in Figure 6 is adapted to prime the device ready for use to remove air from the fluid connector and the cannula to minimise the risk of introducing air into the patient when the device is employed. The fluid reservoir is also designed to pump an initial dose of the microflow fluid to the insertion site around the electrode's sensing tip as this has the

advantage of reducing the lag time before measurements can be made by rapidly hydrating the site with the microflow fluid. This active priming of the device rapidly establishes a baseline electrode response and provides a hydrated environment around the insertion site which enables electrochemical determinations of analyte concentration to be made.

In a further refinement, the device is adapted to allow the fluid introduced at the electrode insertion site to equilibrate towards body temperature before exiting the device at the subcutaneously implanted cannula. This is achieved by running the fluid connector 26 adjacent the base plate 6 of the device 2 so that it is proximal to the patient's body. The equilibration of the temperature of the fluid also has the advantage of improving the performance of the electrode sensor.

In the preferred embodiment of the device for sensing glucose, the initial hydration of the implant site initiates glucose diffusion from the cellular compartment to the interstitial space in which the sensing tip of the electrode is located. This allows the measurement of glucose levels to begin more rapidly than would otherwise be possible, without the priming effect of the microflow fluid. Once hydrated under the initial pressure of the priming pouch, further microflow fluid is drawn to the site by the body's inherent negative tissue pressure, providing a slow flow of fluid across the sensor tip, typically at rates in the order of 30-60 µl/hour, serving to continue hydration of the insertion site and improving the diffusion of glucose to the sensor tip. The slow flow of microflow fluid also continues to prevent fouling of the sensitive sensor tip through deposition of protein

and colloid material from the medium under investigation.

In a further aspect, the construction of the device makes it possible to deliver pharmacologically active agents to the patient via the cannula. In particular, this has the advantage of allowing an agent to be introduced under the direct feedback control of the monitoring device used to control the sensor. Use of the sensor output via appropriate monitoring software can be used to selectively control delivery valves that can permit measured dosing of drugs or other agents. In the preferred application of the invention for glucose monitoring in a diabetic patient, the feedback control could be employed to direct addition of insulin or a drug for treating diabetes in response to either a hypo- or hyperglycaemic episode. As the device is capable of providing continuous real time monitoring of interstitial glucose levels, this allows greatly improved management of diabetes. Thus, long term use of the device may help to ameliorate many of the long term complications associated with diabetes and in particular the comparatively crude level of control that conventional monitoring and treatment are able to provide. However, it will be readily apparent that this use of monitoring and feedback using the device can be used in other situations such as environmental monitoring, bioprocess monitoring or in other applications apparent to those skilled in the art.

The references mentioned herein are all expressly incorporated by reference.

Claims:

1. An electrode device comprising:

an electrode assembly for insertion into a patient, the electrode assembly comprising an electrode having a sensing surface, a cannula for supplying fluid over the sensing surface and a trocar for enabling insertion of the electrode assembly, wherein the electrode is retained within the trocar and the trocar is moveable between an extended position and a retracted position such that in the retracted position, the sensing surface of the electrode extends beyond the trocar;

a body portion in which the electrode assembly is mounted, the body portion including a trocar retraction mechanism operable by a user of the device to cause withdrawal of the trocar to the retracted position when the electrode assembly has been inserted in the patient.

2. The electrode device according to claim 1, wherein the electrode assembly including the trocar is fixed at an angle of between 20° and 40° to the base plate and the trocar extends beyond the base plate to provide an insertion depth of about 5 mm.

3. The electrode device according to claim 1 or claim 2, wherein the cannula, trocar and electrode assembly are arranged concentrically.

4. The electrode device according to any one of claims 1 to 3, wherein the trocar retraction mechanism comprises a retraction arm attached to the body of the device which is moveable to cause retraction of the trocar.

5. The electrode device according to claim 4, wherein the body portion of the electrode device is provided with

a base plate for seating the device against the patient and the retraction arm is pivotally attached to the body of the device, such that the retraction arm is moveable from a first position in which the trocar is extended to a second position in which the trocar is retracted and the retraction arm is approximately coplanar with the base plate.

6. The electrode device according to claim 5, wherein retraction mechanism further comprises a retraction cord which links the retraction arm to the end of the trocar which is positioned within the body of the device.

7. The electrode device according to any one of claims 1 to 6, which further comprises a cooperating locking formation, such that on retraction of the trocar, the trocar is locked in the retracted position.

8. The electrode device according to claim 7, wherein the cooperating locking formation comprises a tooth or set of teeth associated with the retractor mechanism, and a tooth or set of teeth associated with one or more arms fixed in relation to the body portion, wherein retraction of the trocar causes the first tooth or set of teeth to slide over the second tooth or set of teeth and locks the trocar in the second, retracted position.

9. The electrode device according to any one of claims 1 to 8, which further comprises a locking mechanism to prevent premature retraction of the trocar prior to employment of the device.

10. The electrode device according to claim 9, wherein the locking mechanism comprises a locking pin which is

removed prior to employment of the device.

11. The electrode device according to any one of claims 1 to 10, wherein the electrode comprises a core of a material selected from platinum and platinum iridium.

12. The electrode device according to claim 11, wherein the electrode further comprises a stainless steel sheath surrounding the core, wherein the sensing surface is located on the core and the sensing surface extends beyond the stainless steel sheath.

13. The electrode device according to any one of claims 1 to 12 wherein the sensing surface comprises immobilised enzyme.

14. The electrode device according to claim 13, wherein the immobilised enzyme forms a layer on the sensing surface, and the sensing surface further comprises an interferent rejection layer between the core and the enzyme layer, and an diffusion limiting layer overlying the enzyme layer.

15. The electrode device according to claim 13 or claim 14, wherein the enzyme is glucose oxidase.

16. The electrode device according to any one of claims 1 to 15, further comprising a control and read-out device, for making a determination of analyte concentrations using the electrode and displaying the results to users of the device.

17. The electrode device according to any one of claims 1 to 16, further comprising a fluid delivery device for supplying fluid to the cannula.

18. The electrode device according to claim 17, wherein the fluid delivery device supplies fluid to the cannula at a rate such that a microflow of liquid is established over the sensing surface, wherein analyte is able to diffuse towards the electrode at a rate faster than the microflow carries it away.

19. The electrode device according to claim 18, wherein the microflow of liquid over the sensing surface has a rate of 30 to 60µl/h.

20. The electrode device according to any one of claims 17 to 19, wherein the fluid delivery device comprises a fluid supply bag containing fluid and having a port; and a casing adapted to receive the fluid supply bag, the casing including one or more formations adapted to exert pressure on the fluid in the bag to cause an initial supply of fluid to remove air from the electrode device and to provide fluid at the site of insertion of the electrode, and thereafter to supply fluid at a lower flow rate.

21. The electrode device according to any one of claims 17 to 20, further comprising a chamber or length of tubing between the fluid delivery device and the cannula.

22. The electrode device according to any one of claims 17 to 21, wherein the fluid comprises one or more agents selected from the group consisting of a pharmacologically active agent, an anticoagulant, an agent for modulating the viscosity of fluid, an analgesic, one or components of a buffering system, an isotonicising agent, an anti-inflammatory agent, a preservative, a sterilising agent,

an agent to render tissues more permeable to liquids or electrolytes, and an antibiotic.

23. The electrode device according to any one of claims 1 to 22, further comprising a drug delivery device, the drug delivery device comprising a controller for receiving analyte concentration data from the electrode device and a drug reservoir for providing doses of drug to the patient.

24. The electrode device according to claim 23, wherein the drug is insulin.

25. A kit comprising an electrode device according to any one of claims 1 to 16 and a sealed bag containing sterile fluid, wherein the sealed bag comprises a port and the electrode device comprises a connector adapted to form a fluid connection with the port, such that the seal between the port and the connector is airtight.

26. The kit according to claim 25, wherein port is sealed by a membrane and the connector is adapted to pierce the membrane, such that when the connector pierces the membrane, the membrane forms an airtight seal around the connector.

27. The kit according to claim 25 or claim 26, further comprising a casing adapted to receive the fluid supply bag, the casing including one or more formations adapted to exert pressure on the fluid in the bag to cause an initial supply of fluid to remove air from the electrode device and to provide fluid at the site of insertion of the electrode, and thereafter to supply fluid at a lower flow rate.

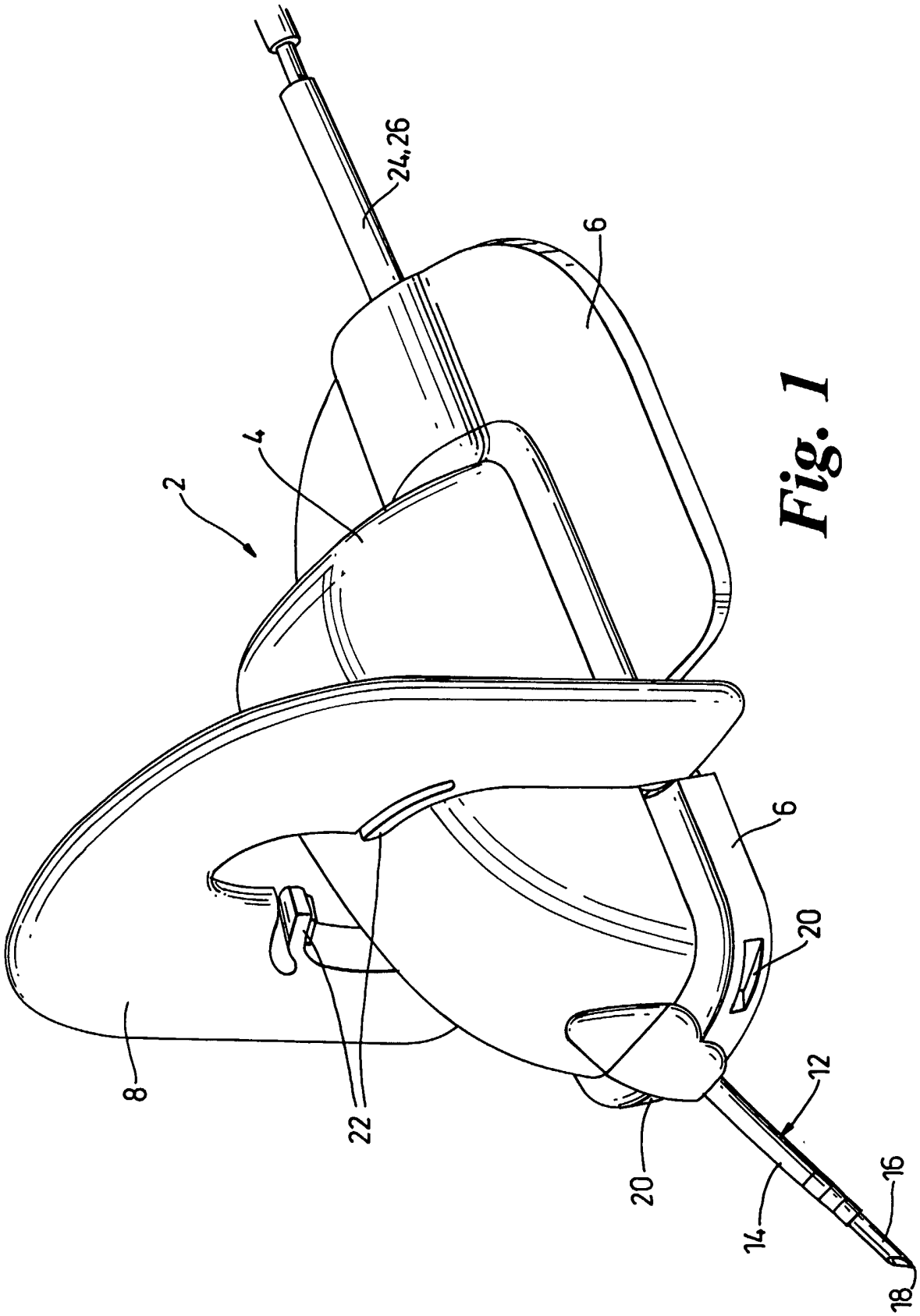


Fig. 1

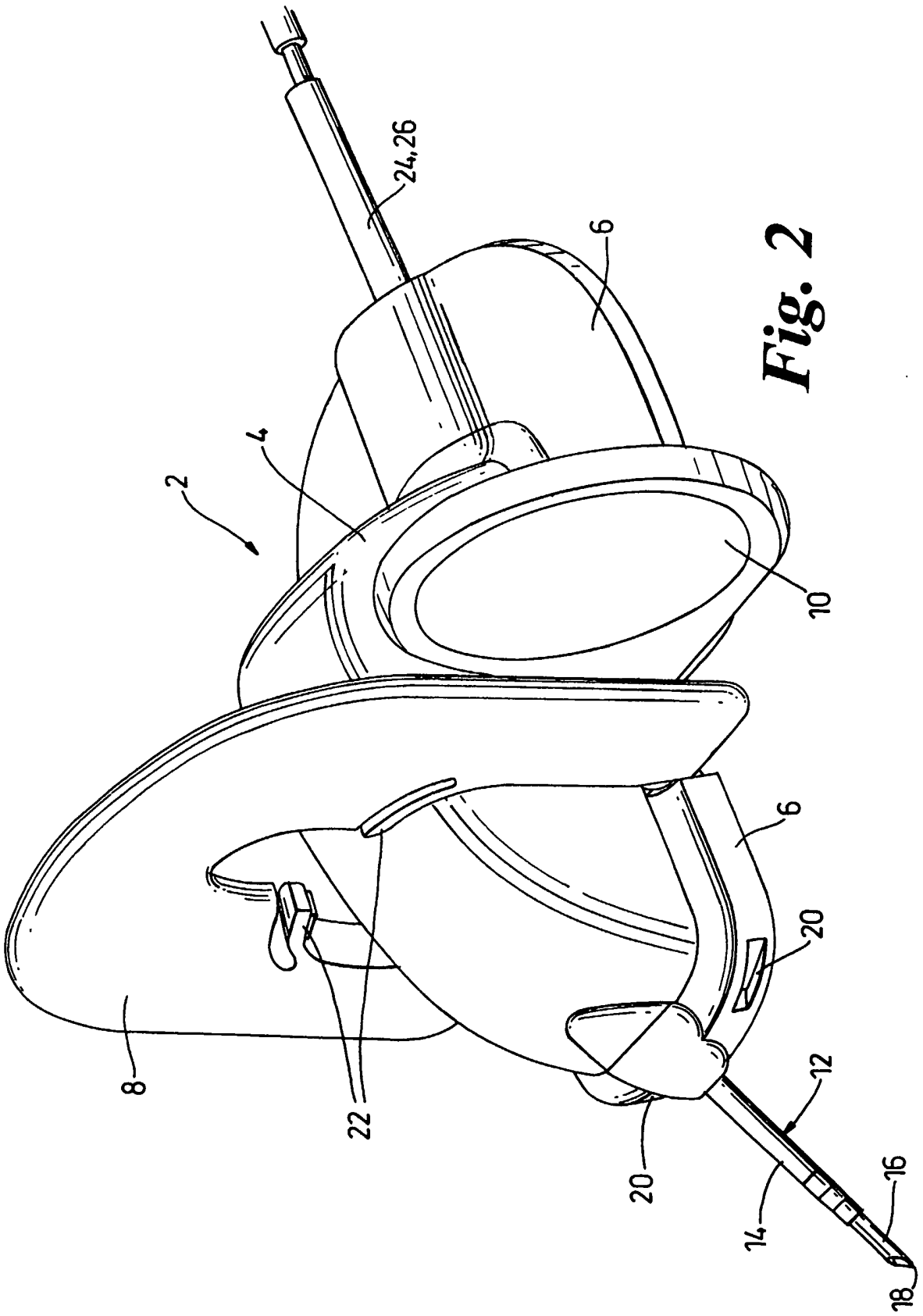


Fig. 2

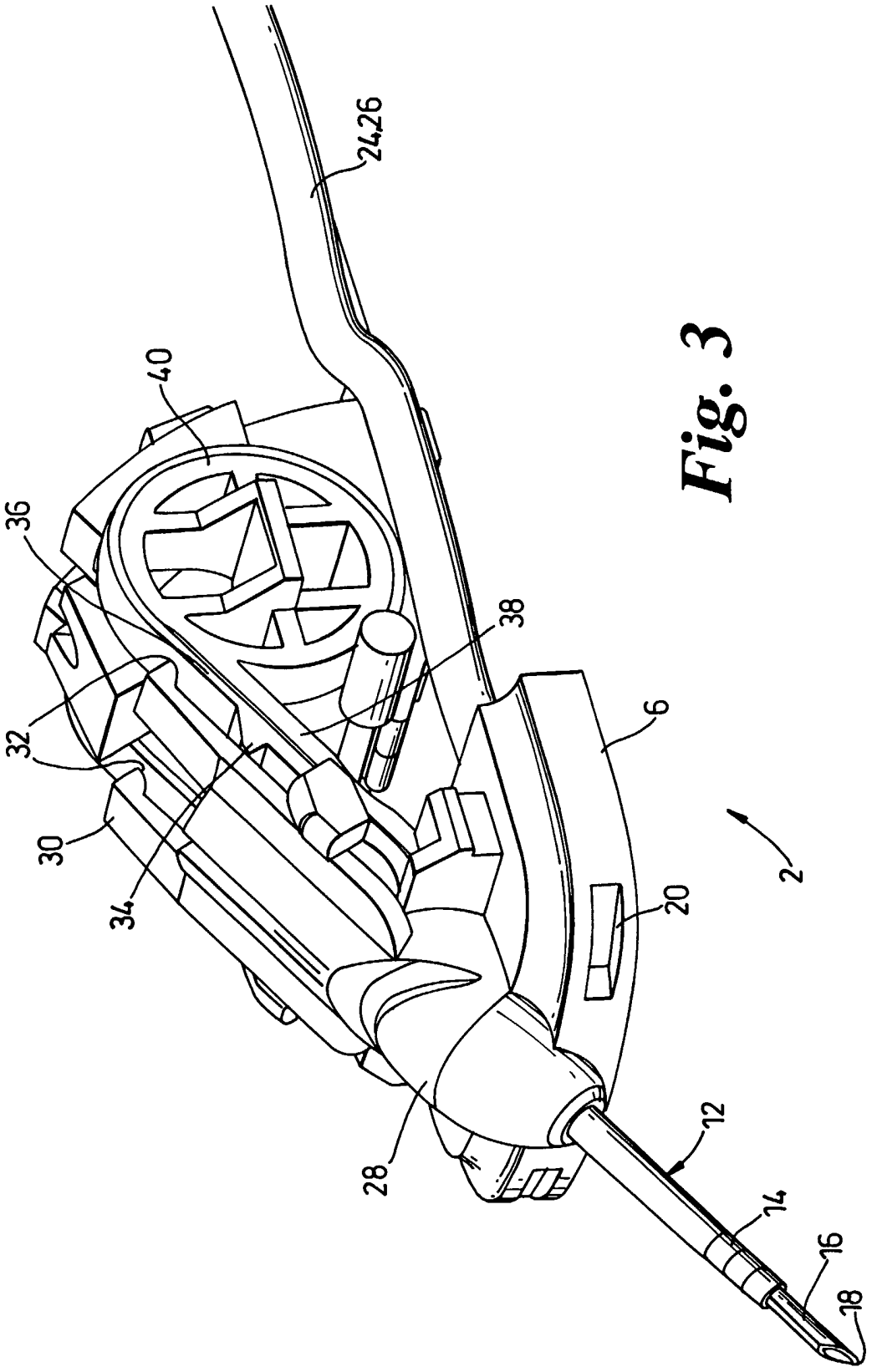


Fig. 3

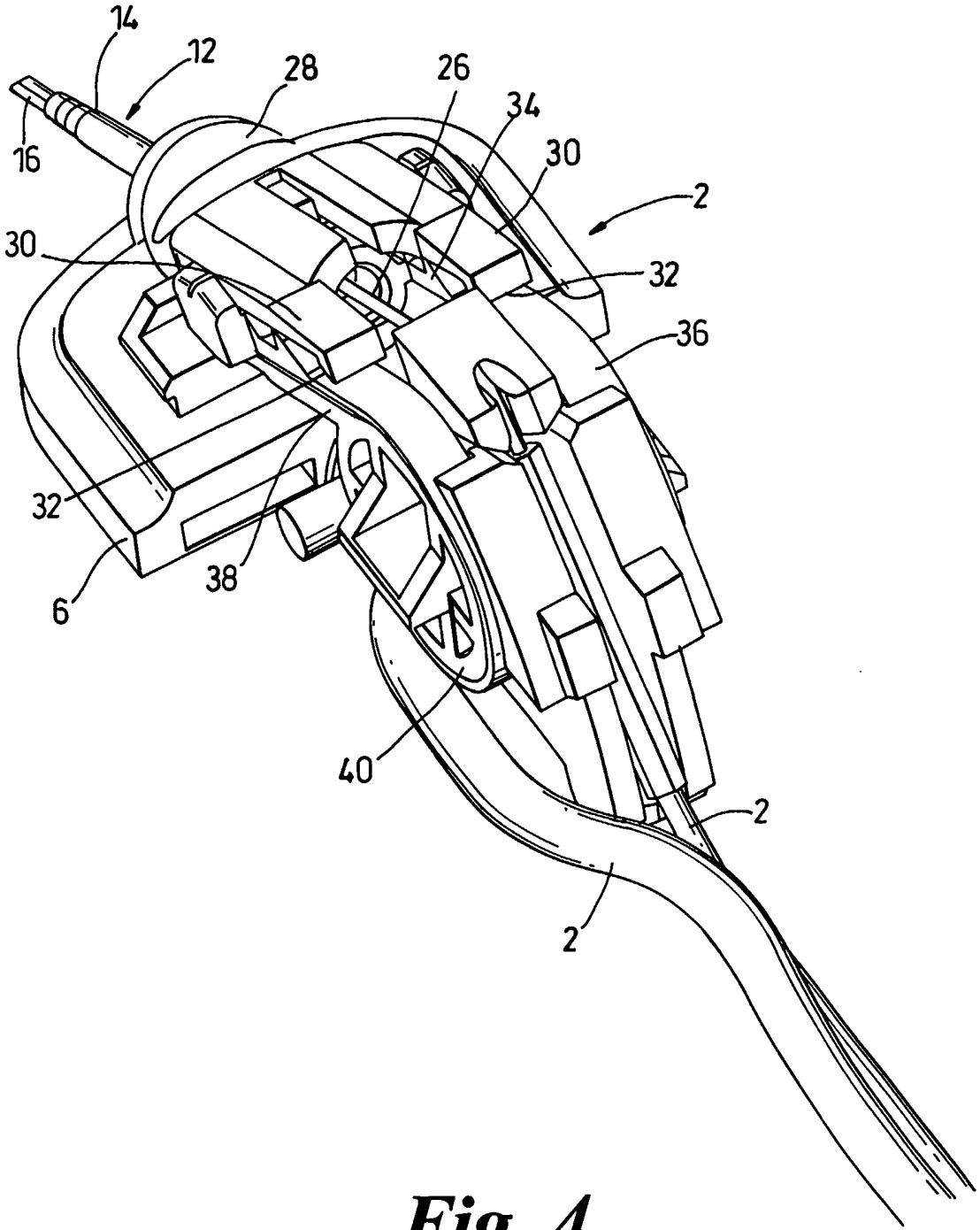
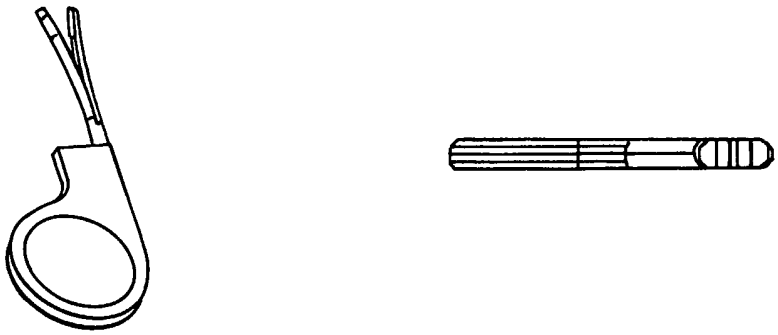


Fig. 4



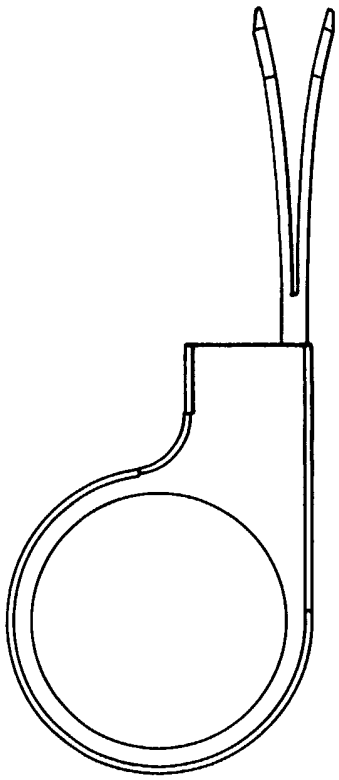


Fig. 5

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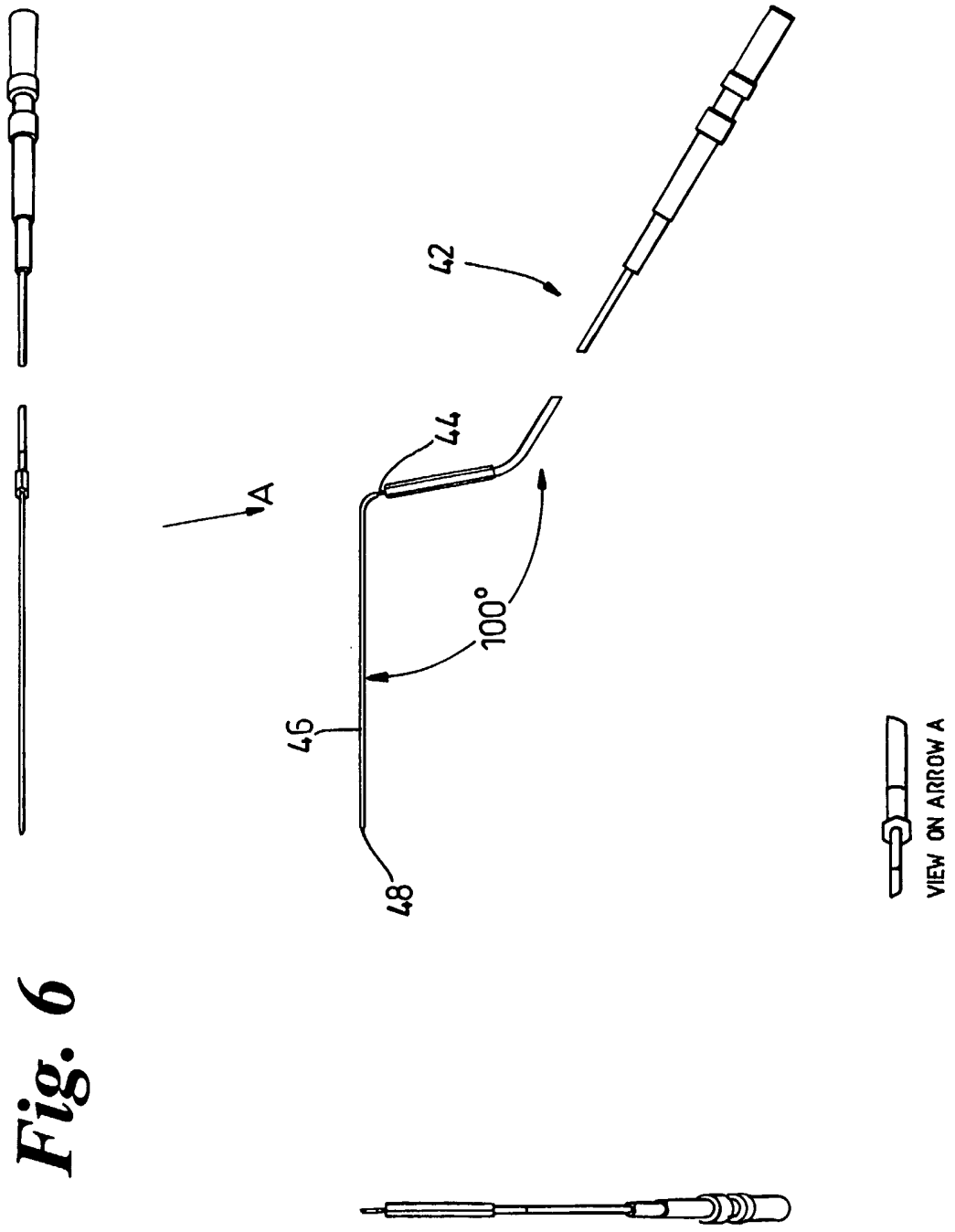


Fig. 6

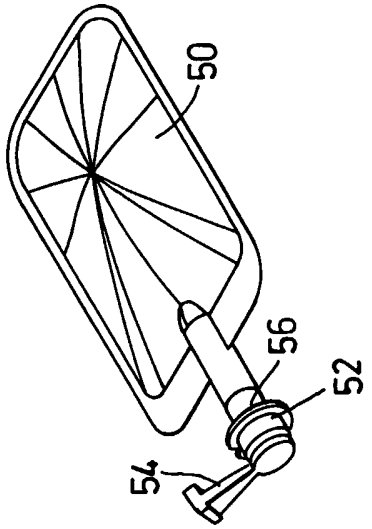
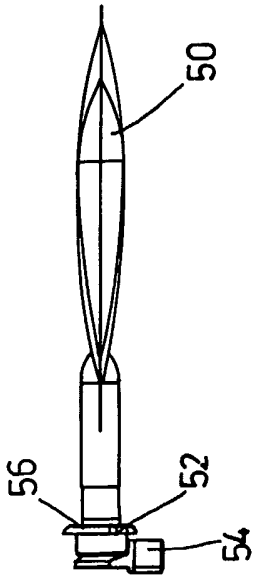
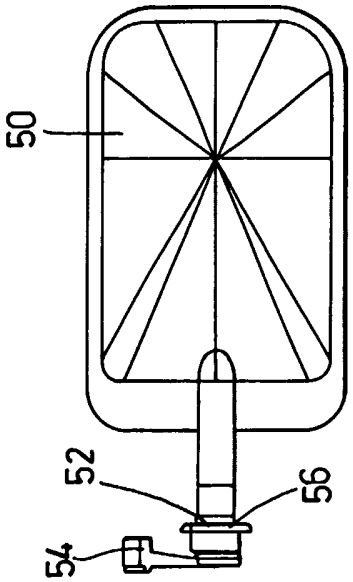


Fig. 7





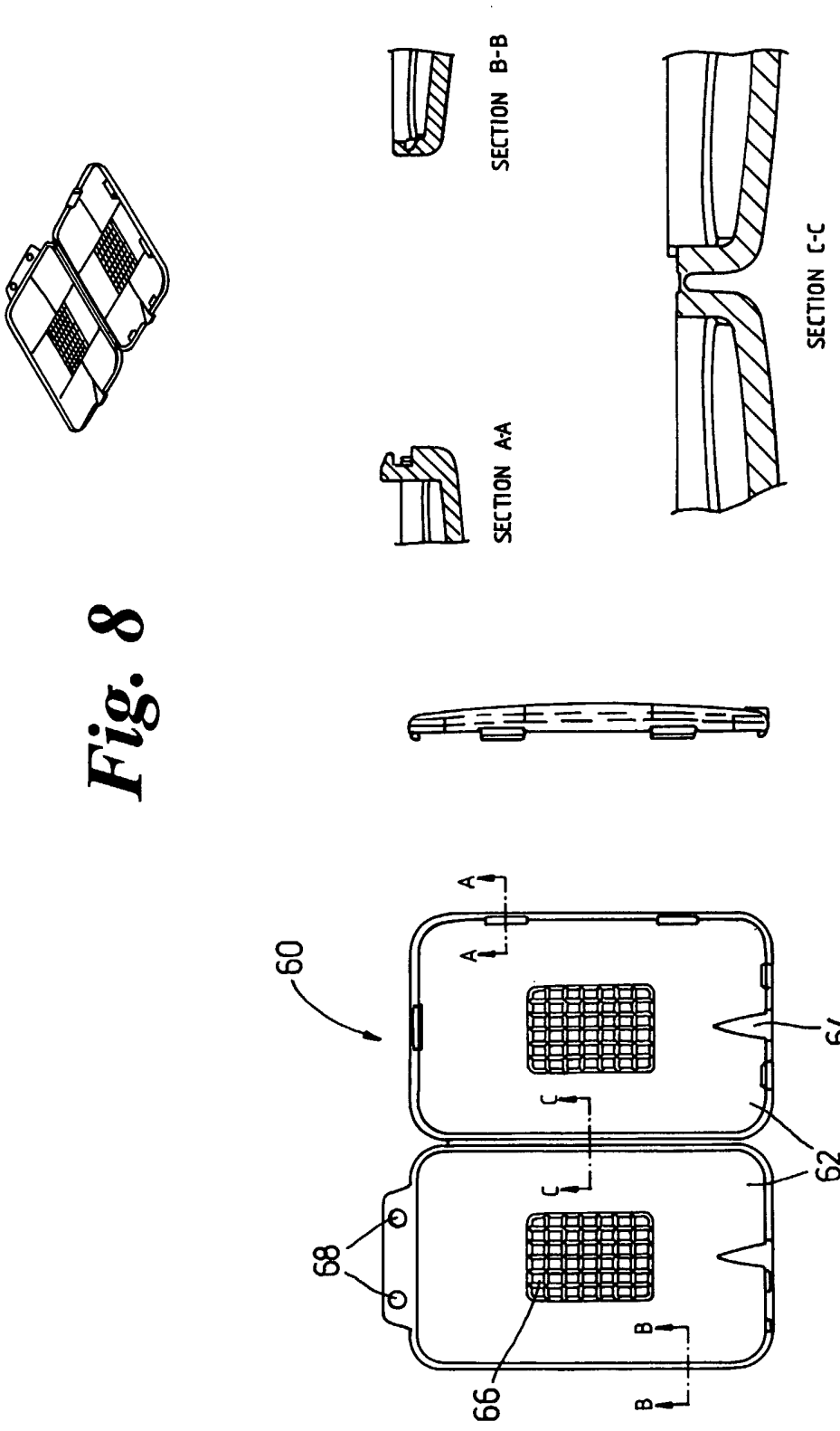


Fig. 8

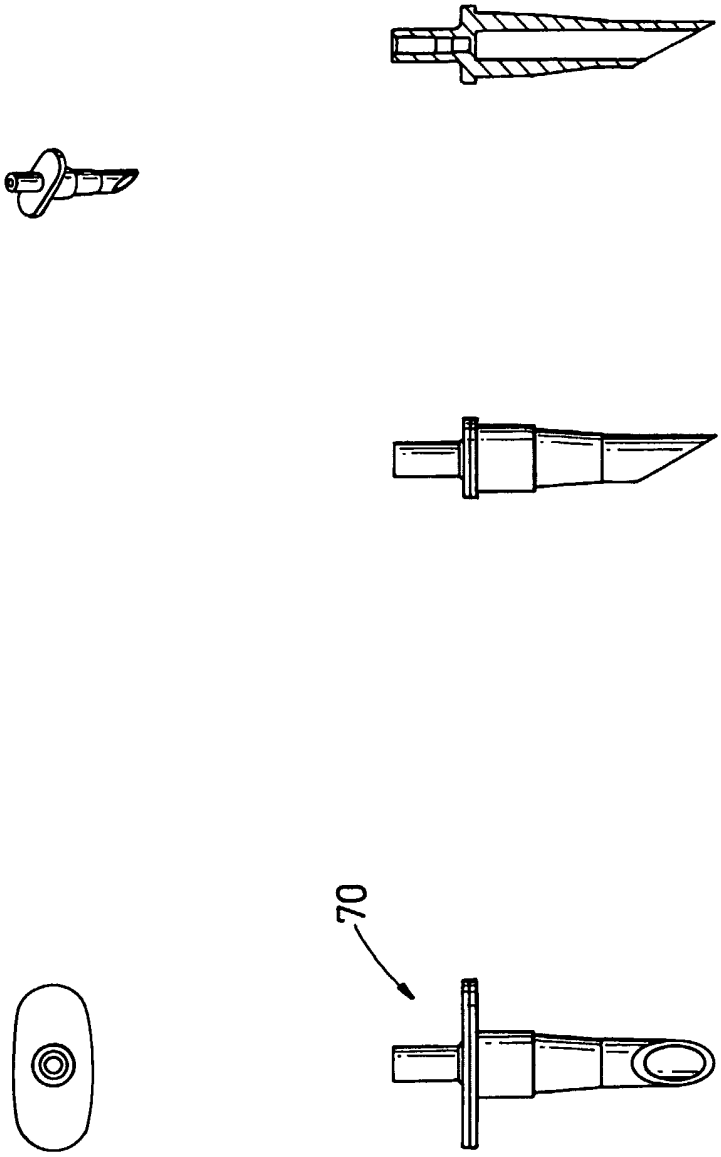


Fig. 9

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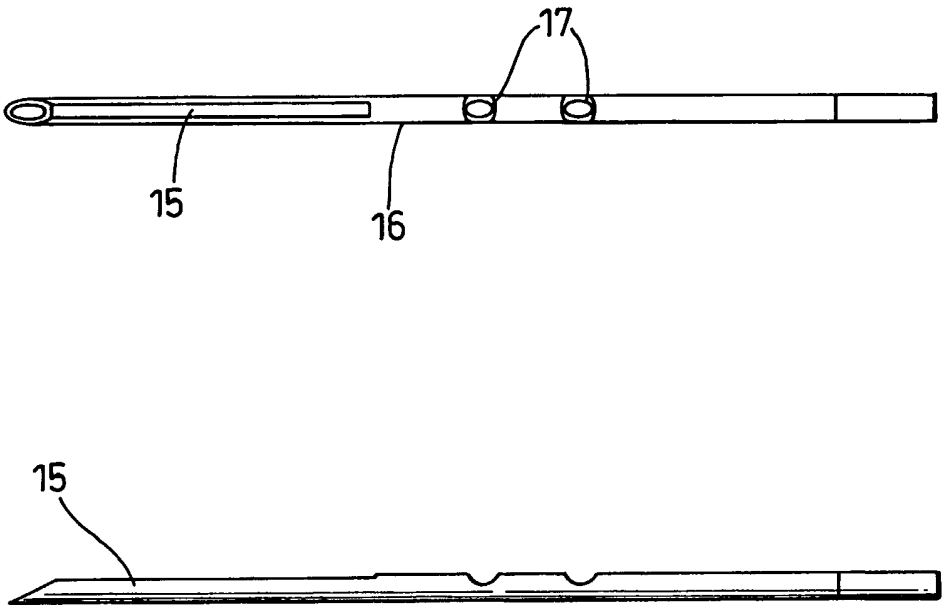

Fig. 10

INTERNATIONAL SEARCH REPORT

tional Application No
PCT/GB 02/02632

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61B5/00 A61B17/34

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61B

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 practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 954 643 A (VANANTWERP NANNETTE M ET AL) 21 September 1999 (1999-09-21) column 1, line 62 -column 3, line 3; figures 1,3	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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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
1 October 2002	16/10/2002

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, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gaillard, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/GB 02/02632

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5954643 A	21-09-1999	EP 0987982 A1	29-03-2000
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