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(54) **SYSTEM FOR MONITORING THE CONCENTRATION OF ANALYTES IN BODY FLUIDS**

SYSTEM ZUR ÜBERWACHUNG DER KONZENTRATION VON ANALYTEN IN KÖRPERFLÜSSIGKEITEN

SYSTEME PERMETTANT DE CONTROLER LA CONCENTRATION D'ANALYTES DANS DES FLUIDES CORPORELS

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Description

[0001] The present invention is in the field of diagnosis in which body fluids are withdrawn and analysed for the presence or concentration of analytes.

[0002] Numerous methods are known in the prior art for monitoring analyte concentrations in body fluids. On the one hand there are systems in which blood is withdrawn by a catheter and conveyed to a measuring cell. The document WO 91/16416 which describes an instrument that can be carried on the arm that withdraws blood samples by means of a catheter implanted in a blood vessel is mentioned as a representative of such procedures. The sample liquid is conveyed through an essentially closed channel system to an enzyme electrode which is designed to carry out a multitude of measurements. The system described in this document and other systems based on electrochemical sensors that measure continuously, have the disadvantage that the sensors have a pronounced signal drift. This becomes particularly obvious from the document WO 91/16416 when the laborious calibration is taken into consideration. Another disadvantage of such sensor-based systems is that relatively large amounts of fluids are required. In the prior art sensors are known as systems that only require small amounts of liquid and thus this statement is initially surprising. However, when emphasising the positive features of sensor systems, one often does not take into account that fluid channels are necessary and a sensor surface of sufficient size has to be wetted.

[0003] Ultrafiltration devices are also known in the prior art of which the documents US 4,832,034 and US 4,777,953 are mentioned as examples. These systems also use electrochemical sensors and thus also have the above-mentioned disadvantages. In addition there are disadvantages which are caused by the ultrafiltration membrane. It is critical to select a suitable membrane material which has the combined properties of an adequately high filtration effect and permeability and does not already become blocked after a short period.

[0004] Another procedure for monitoring analyte concentrations is known under the name microdialysis. Representative documents from this field are: US 5,174,291, EP 0 401 179 and US 4,265,249. Flow measuring cells with electrochemical sensors are used in the arrangements described in these documents. Although the ultrafiltration problems caused by membranes are less with microdialysis, microdialysis systems have the disadvantage that a perfusion liquid has to be pumped through a hollow catheter. The provision of solutions, the pumping process and the construction of the catheter are technical complications which increase the complexity.

[0005] The methods described above for monitoring analyte concentrations in body fluids are based on the premise that the monitoring requires a continuous or at least a more or less continuous measurement at relatively short time intervals. This explains the exclusive use of sensors that operate continuously in flow measuring cells.

[0006] Discontinuous concepts are also known in the field of analyte concentration monitoring. For example diabetics carry out several discrete measurements during a day in order to monitor their blood glucose level. For this purpose is it customary to firstly make an incision with a lancet and to apply the emerging blood to a disposable test element. This is analysed with a suitable device in order to determine the blood glucose concentration. Optical systems as well as systems that use electrochemical test elements are known in the prior art. Devices have also been known for some time in which the incision, sample collection and sample application can be carried out with a single disposable test element. Such systems for determining blood glucose in interstitial fluid are described for example in the documents US 5,746,217, US 5,823,973 and US 5,820,570. The aforementioned devices have a thin cannula which is inserted into the dermis and collects interstitial fluid at this site. The cannula conveys the liquid onto a test element. A disadvantage of this system is that a cannula has to be inserted again for each individual measurement. In addition to the discomfort caused by the repeated piercing, the user has to carry out a number of operating steps such as inserting a disposable element into an apparatus, starting the lancing process, waiting until the result of the analysis is displayed and replacing the test element. Moreover the said devices have to be carried around by the user and he has to find a discreet place to carry out the measurement if he does not want to publicly exhibit his disease.

[0007] A system which also has the aforementioned disadvantages, but which uses a system comprising a catheter and an initially separate test element is described in US 5,368,029. According to this document a catheter is firstly introduced into a blood vessel and one waits until a transparent chamber is filled with blood (flushing). Then a disposable test element is inserted into the chamber through a valve slit in order to bring the test element into contact with the blood. It is hardly conceivable that such a system could be used routinely by a diabetic since it is necessary to introduce a catheter into a blood vessel with a considerable risk of infection and injury. In addition a relatively large amount of sample is required. The description in the document shows that the system is designed to be used in emergency medicine. Another essential disadvantage of the concept is that the system does not enable monitoring of an analyte concentration but only allows a single measurement which reflects the momentary concentration level. The document contains no information or suggestions whatsoever on how to carry out repeated measurements by coupling new test elements. This is logical since the blood collected in the chamber (33) is not exchanged and thus subsequent measurements with additional test elements would only yield the same measured value and not a measured value that would lead to a later concentration value.

[0008] WO-A-00/22977 discloses a system for monitoring the concentration of analytes in body fluids, in particular interstitial fluids, comprising

a) a catheter having an implantable region and an outlet opening for the withdrawal of body fluid,
b) a first and a second analytical zone which, after contact with the withdrawn fluid, undergo a detectable change when an analyte is present,
c) a device for contacting the first analytical zone with fluid from the catheter and for subsequently contacting the second analytical zone with fluid from the catheter,
d) an analytical device to analyse changes on the analytical zones caused by the analyte-containing fluid in order to determine the concentration of an analyte monitored.

[0009] The present invention is as defined in claim 1 and concerns a system for monitoring the concentration of analytes in body fluids, in particular in interstitial fluid and comprises a catheter with an implantable region and an outlet aperture for withdrawing fluid, in particular body fluid. A first and a second analytical zone, which are areas of a continuous test element, are contacted successively with fluid from the catheter and undergo a detectable change when an analyte is present. The contacting of the analytical zones with fluid can be achieved manually and also preferably automatically by means of a device. A system according to the invention additionally has an analytical device to analyse the analytical zones in order to determine the concentration of the analyte on the basis of the changes caused by the analyte. The present invention additionally concerns a method as defined in claim 8, a kit as defined in claim 20 and magazines with test zones as defined in claim 12.

[0010] The present invention combines the advantages of continuously operating systems with those of individual measurements using disposable test elements. The invention utilizes a catheter which remains implanted between the (at least two) measurements and hence it is not necessary to make repeated incisions as is the case with previous systems with disposable test elements. Problems of previous continuously operating systems which are mainly coupled to the use of continuously operating sensors are avoided by using separate test elements. However, this combination of known elements has neither been previously described in the prior art nor made obvious to a person skilled in the art. Previously experts have assumed that measurements have to be carried out at short time intervals for a continuous monitoring of the analyte concentration which necessitates the use of flow measuring cells containing continuously operating sensor systems. Initially the provision of such a large number of analyses at short time intervals appears to be incompatible with disposable test elements. The concept according to the invention revolutionizes the monitoring of analyte concentrations because the monitoring can be carried out with a relatively simple system which is in particular free from the drift of electrochemical sensors. Dry chemistry test elements can be used for the test elements or test zones which have already proven in practice to be particularly suitable with regard to accuracy and precision and are advantageous to manufacture.

[0011] The system and method according to the invention are used to monitor analyte concentrations in body fluids. Analytes that can be monitored using the present invention are for example glucose, lactate, electrolytes, pharmaceutically active substances and such like. Body fluids in the sense of the invention are in particular interstitial fluid and blood. If interstitial fluid is used, fluid is preferred which has been obtained from a depth of > 1 mm under the skin surface since at this position there is a good and sufficiently fast exchange with the blood transport system.

[0012] A catheter with an implantable region is used to withdraw fluid. Catheters within the sense of this invention are tubes into which the body fluid enters and can be removed from an outlet opening and also devices with a semipermeable membrane and hence the fluid entering the catheter is not a body fluid in a strict sense but a fluid that has already been pretreated (ultrafiltrate). In principle it is also possible to use a microdialysis catheter as a catheter which operates with perfusion fluid and takes up analyte from the interior of the body by diffusion and yields dialysate. Catheters with a semipermeable membrane or a microprorous wall have the advantage that cells and even larger molecules interfering with detection may be excluded. It is therefore preferred to employ membranes or microprorous walls with a pore size below 500nm.

[0013] However, a problem with a microdialysis catheter circulating dialysis fluid is that fluid emerging from the catheter may under certain circumstances not reflect the true analyte concentration inside the body but rather only a fraction thereof when the residence times are short. Consequently catheters are preferred for the invention which are designed such that body fluid flows directly out of them (as e.g. in case of ultrafiltration) which may also be freed from cells.

[0014] The term catheter is used in the scope of this invention not only for the part that is implanted in the body but rather the term catheter should also encompass the fluid connections and other connected parts that belong to such a part. In the simplest case the catheter can be composed of a thin hollow needle or a tubing one end of which is inserted into the body and from the other end of which, the outlet opening, a body fluid flows out. Tubing or such like can be coupled to such a catheter so that as a result the outlet opening is shifted to the corresponding end of the tubing. The structure and function of suitable or preferred catheters is described in more detail in conjunction with the figures. It may be advantageous to use a so-called applicator device to insert the implantable region of the catheter into the body. In this manner it is

also possible to construct the implantable region with a very small diameter down to e.g. 100 μm. Even materials like steel are flexible in this thickness range. If an applicator device were not used, flexible constructions would have been eliminated for practical reasons due to the impossibility of introducing them into the body. Suitable applicator devices for flexible and also for rigid arrangements are known in the prior art. US 3,651,807; EP A 0 366 336; WO 95/20991 and WO 97/14468 are herewith referred to as examples where suitable applicator devices are described.

[0015] An additional feature of the invention is the use of two or more analytical zones which undergo a detectable change after contact with the fluid taken from the outlet opening. Diverse forms of suitable analytical zones are known from the field of disposable test elements. Analytical zones which undergo an optically detectable change are particularly preferred in the scope of the invention for reasons which will be described in more detail. An embodiment of the analytical detection zone that is particularly preferred within the scope of the invention is described in US 6,029,919. With regard to the layers of the test element it is of course also possible to use less complex test elements. Electrochemical test elements can also be used for the invention. Electrochemical test elements such as those described in US 5,288,636 are advantageous compared to measuring cells that operate continuously like those used in the field of ultrafiltration and microdialysis since the drift problem is eliminated.

[0016] The use of the term "analytical zone" in contrast to "test element" makes it clear that the analytical zones do not necessarily have to be elements that are separated from one another but that the test zones can indeed be disposed on the same body (test element). In a particularly preferred embodiment of the system according to the invention a tape is used in which the test chemistry is arranged in a band shape and adjacent regions of the tape can be contacted with fluid emerging from the catheter. This also makes it clear that the term analytical zone is not limited to embodiments in which the analytical zones are predefined but that embodiments according to the present invention are particularly advantageous in which the respective analytical zone is not defined until contact with the fluid. As a result positioning problems can be largely circumvented. On the other hand it is, however, also possible to use test elements which are separated from one another, each of which provides one or several analytical zones. As already elucidated according to the present invention disposable embodiments are used for the analytical zones in which an analytical zone that has been used once is not used again. As already eluded to, the analytical zones of the present invention exhibit no drift like that which occurs in the case of flow measuring cells. This is due to the fact that an unused analytical zone is employed and the properties of the analytical zones can be adequately controlled by the manufacturing process as is well-known in the prior art. As a result it is also possible to determine the manufacturing tolerances of the analytical zones at the factory and to store these for example in the form of a bar code in order to increase the accuracy of the analysis by taking into account these variations in the analytical process.

[0017] An important aspect of the present invention is a sequential application of liquid onto test zones in order to contact the test zones with liquid from the catheter. This can be achieved especially by bringing together various analytical zones with the outlet opening of the catheter in order to contact the analytical zones with fluid. Bringing together in this sense primarily means moving the analytical zones to the outlet opening so that they can take up fluid there. If, however, the outlet openings are located on a flexible tube it is possible to guide the outlet opening to an analytical zone for the contacting. The term "bringing together" is also intended to encompass processes in which analytical zones for example in the form of a tape, are conveyed past the outlet opening, (while being in contact with the outlet opening or in direct proximity) in order to apply liquid to the analytical zones.

[0018] Embodiments are also possible in which liquid is already removed from the catheter by contact alone. This can be achieved in particular with absorbent or capillary-active analytical zones. However, it is advantageous to design the system such that liquid does not emerge from the outlet opening until an underpressure is applied. This enables the application of liquid on the analytical zone to be controlled by regulating the pressure conditions in the system.

[0019] Another method of contacting the analytical zones with liquid from the catheter is to move the liquid out of the catheter in portions (dropwise) in such a manner that the fluid portions hit the test zones. This can be achieved in particular by using ink-jet or bubble-jet systems in which the fluid portions are ejected from an outlet opening of the catheter or from a subsequent ejection unit. Reference is made to the well-known printing technologies and to the document US 4,336,544 with regard to a possible design for such an ejection unit.

[0020] As already described in connection with US 5,368,029, it is important for monitoring time-dependent changes of the analyte concentration to ensure that liquid of a defined time range reaches an analytical zone and that this liquid is mixed with the least possible amount of liquid from previous time intervals. This can be achieved by the present invention in a comparatively simple manner by using a catheter with an inner cross-section of less than about 0.5 mm. With such small cross-sections there is almost no convection so that liquid moves through the catheter in the form of a bolus. In this connection it is also important to avoid dead volumes in the catheter as far as possible that are caused for example by back tapers at fluid junctions etc.. Another measure which is important in this connection relates to the ratio between the volume of liquid that is removed from the catheter and the active inner volume of the catheter. The quantity of liquid that is removed is preferably essentially the same as or larger than the active catheter inner volume such

that the active volume is essentially completely emptied when liquid is removed for application onto an analytical zone. This ensures, on the one hand, that the withdrawn liquid is derived from the time interval between the current withdrawal and the previous withdrawal. The active catheter inner volume refers to the inner space of the catheter which fills with liquid between two liquid withdrawals and which is emptied during a withdrawal. In addition to the geometric design of the catheter inner space, the active catheter inner volume is also determined by liquid barriers such as hydrophobic barriers. Preferred designs of the catheter and the withdrawal processes are elucidated below on the basis of figures.

[0021] Another feature of the invention is an analytical device for analysing the analytical zones after contact with liquid. Such analytical devices are well-known in the prior art for example for blood sugar measuring instruments. Reference is herewith made to the document US 4,852,025 as an example thereof in which transformation of reflection-photometric measurements into concentration values is described. Such an analytical device comprises a light source to illuminate an analytical zone, a detector to detect radiation reflected from the analytical zone and an electronic circuit to convert the detector signals into analyte concentrations. Such an analytical device or an additional application detection device can also advantageously be used to determine whether the analytical zone has been adequately contacted with liquid. However, it is not only possible to detect application of liquid as such onto an analytical zone as described for example in EP 0 256 806 but it is also possible to relatively accurately determine the amount of liquid with which the analytical zone has been wetted. A detection of the wetting of an analytical zone is advantageous within the scope of the present invention for several reasons. On the one hand it enables a check of the operating sequence or even a control of the sequence. In the case of systems which operate with an underpressure to allow liquid to flow out of the outlet opening, the detection of a wetting of or an adequate amount of liquid on the analytical zone can for example be used as a signal to switch off the underpressure and thus also the liquid transport. In addition this also enables this signal to be used to break the contact between the analytical zone and liquid or outlet opening.

[0022] Detection of the application of liquid to an analytical zone or detection of the amount of liquid that has been applied to an analytical zone can be achieved in many ways. US 5,114,350 for example describes the monitoring of the surface reflection of a test zone. A similar procedure is also described in US 4,199,261. Furthermore it is known from the document WO 83/00931 that absorbance of radiation by the sample in the infrared range can be used as a measure of the quantity of liquid. The above-mentioned methods can be used within the scope of the present invention.

Figure 1: Construction of a catheter and mode of operation.

Figure 2: Analytical system with a tape-shaped test element in a perspective view.

Figure 3: Cassette with tape-shaped test element and catheter.

Figure 4: Analytical system with a coupling to a tube system for blood withdrawal.

Figure 5: Analytical system with separate units for manual operation.

[0023] Figure 1A shows the construction of a preferred catheter according to the present invention. The catheter comprises a hollow needle the distal part (10) of which is implanted in the tissue (2) of a patient. The hollow needle of figure 1 is manufactured from stainless steel and has an outer diameter of 500 μm, an inner diameter of 100 μm and a length of 7 mm. Plastics can for example also be used instead of stainless steel. A proximal region (11) with an enlarged inner cross section adjoins the distal part of the hollow needle. As shown in figure 1A there is an outlet tube (14) attached to an outlet opening (13) of the hollow needle that is located slightly above the junction region between the implanted region and the proximal region (11). The catheter arrangement is attached by a disk-shaped holder (15) to the body surface. For this purpose the underside of the holder (15) can be provided with an adhesive. In order to further stabilize the arrangement, there is a connecting element (16) above the holder (15) which ensures a fluid-tight coupling of the outlet tube (14) to the outlet opening (13) of the hollow needle (10, 11).

[0024] The function of the catheter arrangement is made clear on the basis of the steps shown in figures A - D. Figure 1A shows that body fluid, in particular interstitial fluid, enters the implanted region (10) of the hollow needle and is conveyed by capillary forces or by vacuum into the proximal part of the hollow needle (11). In order to allow entry of body fluid, the implanted part (10) has one or several inlet openings (17). These can be located on the needle tip as well as in the wall region of the hollow needle located above this. The length of the implanted part and the position of the inlet openings can be used to determine from which depth body fluid is conveyed. It has proven to be advantageous to convey body fluids from depths of more than 1 mm. It was namely found that the upper skin layers (epidermis and dermis) which together have a thickness of about 1 mm only weakly exchange substances with the interior of the body and especially with the blood stream. It has now become standard practice in diabetes monitoring to determine the metabolic state of the diabetic on the basis of the blood glucose value. This is especially due to the fact that the blood stream supplies the brain and thus hypoglycaemia can become an acute threat to life.

[0025] Consequently it is preferred for the present invention to obtain sample liquid from depths of more than 1 mm, preferably from a depth range of 3 to 10 mm.

[0026] As shown in figure 1A the body fluid rises in the hollow needle and fills the proximal part (11) of the hollow needle. This usually takes place solely by means of the capillary forces in the hollow needle. For this purpose it is advantageous when the interior region of the hollow needle that is to be wetted by sample liquid is made hydrophilic. In the case of metallic hollow needles this can for example be achieved by applying a hydrophilizing coating. If the capillary forces are not sufficient an underpressure may be applied to convey body fluid from the interior of the body.

[0027] In figure 1A an air vent (12) is provided at the upper end of the hollow needle which allows air displaced by the body fluid to escape. The air vent is preferably made hydrophobic to prevent body fluid from escaping from the hollow needle. The air vent can for example be a plastic tube made from a hydrophobic polymer such as polyethylene. Another important function of the air vent is to limit evaporation from the hollow needle to avoid blockage of the system by dried up liquid.

[0028] Figure 1B shows the arrangement of figure 1A in a filled state ready for the determination. In particular it can be seen that firstly only the interior space of the hollow needle has been filled but not the connecting tube (14). This is achieved by using a connecting tube which has a hydrophobic (or hydrophobically coated) inner wall. Liquid is withdrawn from the filled state of figure 1B as shown in figures C and D. Application of an underpressure at the outlet opening (14') of the connecting tube (14) empties the upper widened part of the hollow needle (proximal part 11). Preferably the fluid forces in the system are adjusted such that only the hollow space of the needle above the outlet opening (13) is emptied. After this space has been emptied, air is sucked in so that the body fluid is moved in the form of a bolus through the connecting tube onto a test zone which is contacted with the outlet opening (14'). The liquid forms a spot (21) on the test zone (20) which has different optical properties than the surroundings and can thus be detected. After the upper inner space of the needle has been emptied, it can be slowly filled again with liquid which subsequently flows from the implanted part. It was found that measurements at intervals of about 5 minutes are completely adequate for monitoring the glucose concentration in humans so that the time period required to fill the upper part of the needle is relatively uncritical.

[0029] The system shown in figure 1 operates in a batch mode and the volume provided by one discharge can be adjusted by the volume in the upper needle region (11). Alternatively liquid from an implanted needle can be drawn up directly onto a test zone by for example contacting the test zone with an outlet opening.

[0030] Figure 2 shows a system for monitoring concentrations which has a measuring unit (101) and a disposable unit in which test zones are arranged in the form of a test element tape. The connecting tube (114) which can be coupled to the hollow needle as an alternative to the connecting tube (14) in figure 1 is shown on the front side of the disposable unit (121). The unit (121) is closed such that an underpressure relative to the outer space can be applied to its inner space via an underpressure connection (118). Two rollers are located in the interior space of the unit (121), of which the first, the dispenser roller (119) carries a reel of tape-shaped analytical agent. The tape is passed from the first roller (119) behind the outlet of the tube (114) and wound onto the second roller, the waste roller (120). The use of an absorbent analytical tape is particularly advantageous within the scope of the invention since liquid is taken up and absorbed which thus avoids contamination of the interior space and also ensures a hygienic disposal of the fluids. In order to operate the roller mechanism the unit (121) has a rubber collar (122) in which a drive rod rotates which is driven by the measuring unit (101) and which winds the analytical tap onto the roller (120) in a step-wise manner. The measuring unit (101) is equipped with an optical head (102) which is inserted into a recess in the disposable unit (121). The optical head (102) has a light source for illuminating the analytical tape and a detector to record the reflected radiation. For this purpose an optical window (103) is provided on the front side of the optical head (102). Since the analytical tape passes through a region that is closed to the external space and to which underpressure can be applied, a transparent window is provided in the unit (121) between the analytical tape and the optical head. The measuring unit also has an electronic analytical unit to determine analyte concentrations based on the reflected radiation. The results that are determined can for example be shown directly on a display or they are passed onto a data processing unit (130) in order to be displayed or transmitted further. The measuring unit also has a connection (105) for the tube (118) and a pump connected to the connector which can be used to pump air out of the disposable unit (121). The measuring unit (101) additionally has a connector (104) for the rubber flange (122) and a drive mechanism for a drive rod that rotates in the flange. After the measuring unit and disposable unit has been connected together and with a catheter, the analyte concentrations are monitored as follows:

[0031] Underpressure is applied by the pump of the measuring unit to the disposable unit (121) such that body fluid that has collected in the catheter is sucked via the tube (114) into the unit (121) and passes onto the tape-like test element (analytical tape). After the fluid bolus has been applied to the test zone, the analytical optical system (102) is used to check whether the sample has been correctly applied to the test zone on the basis of the wetted spot. A reflection photometric analysis of the test zone is now carried out using the analytical optics (102) and the measurement result is converted into a concentration value for the analyte concentration. In the case of embodiments which do not operate in a batch

mode as described in connection with figure 1, the application of fluid on the test zone can also be monitored and when a sufficient amount of fluid is detected, the contact between the test zone and fluid can be interrupted for example by releasing the underpressure. Usually several minutes elapse after the measurement is completed until a short length of the tape-like test element is wound onto the waste roller (120) by actuating the drive mechanism and thus a fresh test zone is moved to the vicinity of the outlet opening of the tube (114). Then liquid can be conveyed by again applying an underpressure and can be taken up by the fresh analytical zone at the outlet position of the tube (114).

[0032] Figure 3 shows a disposable unit (121') that is similar to the disposable unit shown in figure 2. The hollow needle (110') that can be implanted in the body is already integrated into this disposable unit. The implantable region (110') is arranged perpendicular to the base surface (124') of the disposable unit. As a result it is possible to implant the hollow needle (110') directly in the body by pressing the base surface of the disposable unit on a body surface to simplify the handling. The hollow needle (110') is joined to the connecting tube (114') which is held by a holder (125'). The tape-like test element (108') is guided past the outlet site of the connecting tube (114') to yield the sample application spot (140) at this position. The analytical tape is guided through rollers (126'). If one measurement is carried out every 5 minutes a 100 cm long analytical tape (108') enables the analyte concentration to be monitored over a period of about 24 hours. In order to prevent ageing of the analytical tape (108') during this period, a desiccant (127') can be provided in the disposable unit (121'). Also due to the ageing of the analytical material it is preferable to seal and store the disposable units (121/121') in a water-tight and vapour-tight manner before use. This can be achieved in a simple manner by sealing the disposable units after manufacture in a plastic laminate.

[0033] Figure 4 shows a system for monitoring analyte concentrations which can for example be used in the field of emergency medicine. In this field it is usual to place a catheter in a blood vessel in order to withdraw blood to monitor analyte concentrations or to administer medicines. When a blood stream is withdrawn via a fluid line (200), a system can be coupled to it so that the analyte concentration can be monitored directly in the blood. A T-piece (201) can be provided for this via which blood is withdrawn using the withdrawal tube (114"). The monitoring process is similar to that described in the previous figures. However, with the system shown withdrawal is made directly from the blood stream without the batchwise filling and emptying of a hollow space of a predetermined volume as in figure 1.

[0034] Figure 5 shows an embodiment of a monitoring system that is integrated to a lesser degree. The unit (301) carried on the body comprises a catheter (310) that can be implanted in body tissue (2) which is held in a plate (315) that is attached to the body. A holder (302) for test elements with a receiving opening (303) is located above the catheter opening. When a first test element (320) is inserted, the analytical zone (321) is placed above the catheter opening and body fluid emerging from the catheter wets the analytical zone. When a sufficient amount of body fluid has been applied to the test zone which an for example be visually detected by the user, the test element is inserted manually into a conventional analytical instrument (400) and analysed there. As soon as an additional measurement is required, the user can insert a second test element (320') into the opening (303) to wet the test zone (321'). Although the user has to carry out more steps on his own than is the case with a system shown in the previous figures, the embodiment of figure 5 has an extremely simple construction and it is possible to use commercially available units for test elements and analytical instruments. A major advantage of the system of figure 5 compared to previous commercial systems is that the operator does not have to repeatedly pierce his body for the individual withdrawals of body fluid, but instead the unit (301) provides the necessary body fluid for the analyses as required.

Claims

1. System for monitoring the concentration of analytes in body fluids, in particular in interstitial fluid, comprising

   a) a catheter having an implantable region (10, 110') and an outlet opening (13) for the withdrawal of fluid, in particular body fluid,
   b) a first and a second analytical zone which, after contact with the withdrawn fluid, undergo a detectable change when an analyte is present in the fluid, wherein said first and second analytical zones are disposable such that an analytical zone that has been used once is not used again
   c) a device for contacting the first analytical zone with fluid from the catheter and for subsequently contacting the second analytical zone with fluid from the catheter,
   d) an analytical device to analyse the changes on the analytical zones caused by the analyte-containing fluid in order to determine the concentration of an analyte to be monitored

   wherein the first and second analytical zone are areas of a continuous test element, preferably of a tape (108').

2. System as claimed in claim 1, in which the contacting is carried out by bringing together the outlet opening and the first and second analytical zone.

3. System as claimed in claim 1, in which the analytical

zones are contacted by moving portions of fluid out of the catheter onto the first and second analytical zone by means of an ejector unit.

4. System as claimed in claim 1, in which the first and second analytical zone are separate objects that are attached to a common support.

5. System as claimed in claim 1, in which an underpressure is applied to the outlet opening in order to convey liquid.

6. System as claimed in claim 1 or 5, in which the catheter is designed such that no liquid emerges from the outlet opening until an underpressure is applied to the outlet opening.

7. System as claimed in claim 1, 5 or 6 in which the bringing together of the analytical zone and outlet opening is synchronised with the application of an underpressure such that liquid emerging from the outlet opening is taken up by the analytical zone.

8. System as claimed in claim 1, in which the said analytical device or an additional application detection device detects the presence of fluid or the presence of an adequate amount of fluid in or on an analytical zone and interrupts further contact of the analytical zone with fluid.

9. System as claimed in claim 5, in which the said analytical device or an additional application detection device detects the presence of fluid or the presence of an adequate amount of fluid in or on an analytical zone and interrupts the application of the underpressure to the outlet opening.

10. System as claimed in claim 1 comprising a control device which synchronises the bringing together of the first and second analytical zone with the outlet opening.

11. System as claimed in claim 1, 8 or 9 in which the amount of fluid taken up by an analytical zone is essentially equal to or more than the active inner volume of the catheter.

12. System as claimed in claim 1, in which the catheter is designed to remain implanted between contact with the first and second analytical zone.

13. System as claimed in claim 1, in which the system comprises a carrying unit for carrying the system on the body and a magazine in which the analytical zones are disposed which is designed to be inserted into the carrying unit.

14. System as claimed in claim 1, in which the amount of fluid taken up by an analytical zone is less than 100 nl and is preferably in the range between 10 and 50 nl.

15. System as claimed in claim 1, in which the analytical device is designed for an optical analysis of analytical zones.

16. Method for monitoring the concentration of analytes in body fluids, in particular in interstitial fluid, comprising the steps

- providing a first and a second analytical zone
- bringing together the first analytical zone with an outlet opening of an implanted catheter in order to contact the first analytical zone with fluid, wherein said first and second analytical zones are disposable such that an analytical zone that has been used once is not used again
- analysing the change caused by analyte-containing fluid on the analytical zone in order to determine the concentration of an analyte to be monitored

wherein the first and second analytical zone are areas of a continuous test element, preferably of a tape (108').

17. Method as claimed in claim 16, in which after the first analytical zone has been contacted with liquid, the second analytical zone is brought together with the outlet opening and contacted with liquid and a change on the second analytical zone caused by analyte-containing liquid is analysed in order to determine the concentration of an analyte to be monitored.

18. Method as claimed in claim 16 or 17 in which the analytical zone is moved manually towards the outlet opening.

19. Method as claimed in claim 16 or 17 in which the analytical zone and outlet opening are brought together by a device.

20. Kit for monitoring the concentration of analytes in body fluids, in particular in interstitial fluid, comprising,

- a carrying unit with a catheter comprising an implantable region and an outlet opening for withdrawing fluid, in particular a body fluid,
- two or more analytical zones for contact with fluid which undergo a detectable change when an analyte is present in the fluid , wherein said first and second analytical zones are disposable such that an analytical zone that has been used once is not used again
- an analytical device located in the carrying unit

or present separately for analysing changes caused by the analyte-containing fluid on the two or more analytical zones in order to determine the concentration of an analyte to be monitored

wherein the first and second analytical zone are areas of a continuous test element, preferably of a tape (108').

21. Kit as claimed in claim 20 having a device for bringing together a first analytical zone with the outlet opening in order to contact the first analytical zone with fluid and for subsequently bringing together the second analytical zone with the outlet opening in order to contact the second analytical zone with fluid.

22. Magazine for analytical zones which

- has an inlet opening for fluid,
- at least one first and a second analytical zone which, after contact with body fluid undergo a detectable change when analyte is present in the body fluid, said first and second analytical zones being disposable such that an analytical zone that has been used once is not used again, and
- a device for bringing the first and second analytical zone near to the inlet opening such that fluid entering the magazine contacts the respective analytical zone

wherein the first and second analytical zone are areas of a continuous test element, preferably of a tape (108').

23. Magazine as claimed in claim 22, which is closed such that an underpressure can be generated in the magazine by sucking air out of the magazine.

24. Magazine as claimed in claim 22 or 23, which has an optical window.

25. Magazine as claimed in claim 22, which has a fluid link to a catheter for removing fluid from a body.

Patentansprüche

1. System zum Überwachen der Konzentration von Analyten in Körperfluiden, insbesondere in interstitiellem Fluid, umfassend

a) einen Katheter mit einem implantierbaren Bereich (10, 110') und einer Auslassöffnung (13) zur Entnahme von Fluid, insbesondere von Körperfluid,
b) einen ersten und einen zweiten Analysebereich, die nach Kontakt mit dem entnommenen Fluid eine nachweisbare Änderung erfahren, wenn in dem Fluid ein Analyt vorhanden ist, wobei der erste und der zweite Analysebereich wegwerfbar sind, so dass ein Analysebereich, der ein Mal verwendet worden ist, nicht erneut verwendet wird,
c) eine Einheit zum Kontaktieren des ersten Analysebereichs mit Fluid aus dem Katheter und zum anschließenden Kontaktieren des zweiten Analysebereichs mit Fluid aus dem Katheter,
d) eine Analyseeinheit zum Analysieren der von dem Analyt enthaltenden Fluid an den Analysebereichen bewirkten Änderungen, um die Konzentration eines zu überwachenden Analyten zu bestimmen,

wobei der erste und der zweite Analysebereich Teile eines kontinuierlichen Prüfelements, vorzugsweise eines Bands (108'), sind.

2. System gemäß Anspruch 1, wobei das Kontaktieren durch Zusammenbringen der Auslassöffnung und des ersten und zweiten Analysebereichs durchgeführt wird.

3. System gemäß Anspruch 1, wobei das Kontaktieren der Analysebereiche durch Hinausbewegen von Fluidportionen aus dem Katheter auf den ersten und zweiten Analysebereich mittels einer Ausstoßeinheit durchgeführt wird.

4. System gemäß Anspruch 1, wobei der erste und der zweite Analysebereich getrennte Gegenstände sind, die auf einem gemeinsamen Träger befestigt sind.

5. System gemäß Anspruch 1, wobei zum Fördern von Flüssigkeit ein Unterdruck an die Auslassöffnung angewandt wird.

6. System gemäß Anspruch 1 oder 5, wobei der Katheter so aufgebaut ist, dass aus der Auslassöffnung keine Flüssigkeit austritt, bis ein Unterdruck an die Auslassöffnung angewandt wird.

7. System gemäß Anspruch 1, 5 oder 6, wobei das Zusammenbringen des Analysebereichs und der Auslassöffnung mit der Anwendung eines Unterdrucks synchronisiert ist, so dass Flüssigkeit, die aus der Auslassöffnung austritt, von dem Analysebereich aufgenommen wird.

8. System gemäß Anspruch 1, wobei die Analyseeinheit oder eine zusätzliche Aufbringungs-Nachweiseinheit das Vorhandensein von Fluid oder das Vorhandensein einer geeigneten Menge Fluid in oder an einem Analysebereich nachweist und einen wei-

teren Kontakt der Analyseeinheit mit Fluid unterbricht.

9. System gemäß Anspruch 5, wobei die Analyseeinheit oder eine zusätzliche Aufbringungs-Nachweiseinheit das Vorhandensein von Fluid oder das Vorhandensein einer geeigneten Menge Fluid in oder an einem Analysebereich nachweist und die Anwendung des Unterdrucks an die Auslassöffnung unterbricht.

10. System gemäß Anspruch 1, umfassend eine Steuereinheit, welche das Zusammenbringen des ersten und des zweiten Analysebereichs mit der Auslassöffnung synchronisiert.

11. System gemäß Anspruch 1, 8 oder 9, wobei die Menge an Fluid, die von einem Analysebereich aufgenommen wird, im Wesentlichen gleich oder größer als das aktive Innenvolumen des Katheters ist.

12. System gemäß Anspruch 1, wobei der Katheter so aufgebaut ist, dass er unter Kontakt mit dem ersten und dem zweiten Analysebereich implantiert bleibt.

13. System gemäß Anspruch 1, wobei das System eine Trägereinheit zum Tragen des Systems am Körper und ein Magazin, in welchem die Analysebereiche angeordnet sind und welches zum Einführen in die Trägereinheit aufgebaut ist, umfasst.

14. System gemäß Anspruch 1, wobei die Menge an Fluid, die von einem Analysebereich aufgenommen wird, kleiner als 100 nl ist und vorzugsweise im Bereich zwischen 10 und 50 nl liegt.

15. System gemäß Anspruch 1, wobei die Analyseeinheit für eine optische Analyse der Analysebereiche aufgebaut ist.

16. Verfahren zum Überwachen der Konzentration von Analyten in Körperfluiden, insbesondere in interstitiellem Fluid, umfassend die Schritte

- Bereitstellen eines ersten und eines zweiten Analysebereichs,
- Zusammenbringen des ersten Analysebereichs mit einer Auslassöffnung eines implantierten Katheters, um den ersten Analysebereich mit Fluid zu kontaktieren, wobei der erste und der zweite Analysebereich wegwerfbar sind, so dass ein Analysebereich, der ein Mal verwendet worden ist, nicht erneut verwendet wird,
- Analysieren der von Analyt enthaltendem Fluid an dem Analysebereich bewirkten Änderung, um die Konzentration eines zu überwachenden Analyten zu bestimmen,

wobei der erste und der zweite Analysebereich Teile eines kontinuierlichen Prüfelements, vorzugsweise eines Bands (108'), sind.

17. Verfahren gemäß Anspruch 16, wobei nach dem Kontaktieren des ersten Analysebereichs mit Flüssigkeit der zweite Analysebereich mit der Auslassöffnung zusammengebracht und mit Flüssigkeit kontaktiert wird und eine von Analyt enthaltender Flüssigkeit an dem zweiten Analysebereich bewirkte Änderung analysiert wird, um die Konzentration eines zu überwachenden Analyten zu bestimmen.

18. Verfahren gemäß Anspruch 16 oder 17, wobei der Analysebereich manuell zu der Auslassöffnung hin bewegt wird.

19. Verfahren gemäß Anspruch 16 oder 17, wobei der Analysebereich und die Auslassöffnung durch eine Einheit zusammengebracht werden.

20. Kit zum Überwachen der Konzentration von Analyten in Körperfluiden, insbesondere in interstitiellem Fluid, umfassend

- eine Trägereinheit mit einem Katheter, umfassend einen implantierbaren Bereich und eine Auslassöffnung zum Entnehmen von Fluid, insbesondere von Körperfluid,
- zwei oder mehrere Analysebereiche zum Kontaktieren mit Fluid, welche eine nachweisbare Änderung erfahren, wenn in dem Fluid ein Analyt vorhanden ist, wobei der erste und der zweite Analysebereich wegwerfbar sind, so dass ein Analysebereich, der ein Mal verwendet worden ist, nicht erneut verwendet wird,
- eine Analyseeinheit, die in der Trägereinheit angeordnet oder getrennt angeordnet ist, zum Analysieren von Änderungen, die von dem Analyt enthaltenden Fluid an den zwei oder mehreren Analysebereichen bewirkt worden sind, um die Konzentration eines zu überwachenden Analyten zu bestimmen, wobei der erste und zweite Analysebereich Teile eines kontinuierlichen Prüfelements, vorzugsweise eines Bands (108'), sind.

21. Kit gemäß Anspruch 20 mit einer Einheit zum Zusammenbringen eines ersten Analysebereichs mit der Auslassöffnung, um den ersten Analysebereich mit Fluid zu kontaktieren, und zum anschließenden Zusammenbringen des zweiten Analysebereichs mit der Auslassöffnung, um den zweiten Analysebereich mit Fluid zu kontaktieren.

22. Magazin für Analysebereiche, welches

- eine Einlassöffnung für Fluid,

- wenigstens einen ersten und einen zweiten Analysebereich, welche nach Kontakt mit Körperfluid eine nachweisbare Änderung erfahren, wenn in dem Körperfluid Analyt vorhanden ist, wobei der erste und der zweite Analysebereich wegwerfbar sind, so dass ein Analysebereich, der ein Mal verwendet worden ist, nicht erneut verwendet wird, und
- eine Einheit, um den ersten und den zweiten Analysebereich in die Nähe der Einlassöffnung zu bringen, so dass Fluid, welches in das Magazin eintritt, den entsprechenden Analysebereich kontaktiert,

umfasst, wobei der erste und zweite Analysebereich Teile eines kontinuierlichen Prüfelements, vorzugsweise eines Bands (108'), sind.

23. Magazin gemäß Anspruch 22, welches so geschlossen ist, dass durch Aussaugen von Luft aus dem Magazin ein Unterdruck in dem Magazin erzeugt werden kann.

24. Magazin gemäß Anspruch 22 oder 23, welches ein optisches Fenster aufweist.

25. Magazin gemäß Anspruch 22, welches eine Fluidverbindung zu einem Katheter zum Entnehmen von Fluid aus einem Körper aufweist.

Revendications

1. Système pour surveiller la concentration d'analytes dans des liquides organiques, en particulier dans le liquide interstitiel, comprenant

a) un cathéter possédant une région implantable (10, 110') et une ouverture de sortie (13) pour le retrait d'un liquide, en particulier d'un liquide organique ;
b) une première et une deuxième zone analytique qui, après la mise en contact avec le liquide retiré, subissent un changement détectable lorsqu'un analyte est présent dans le liquide, lesdites première et deuxième zones analytiques étant jetables de telle sorte qu'une zone analytique qui a été utilisée une fois n'est plus réutilisée ;
c) un dispositif pour la mise en contact de la première zone analytique avec le liquide provenant du cathéter et pour la mise en contact ultérieure de la deuxième zone analytique avec le liquide provenant du cathéter ;
d) un dispositif analytique pour analyser les changements intervenus sur les zones analytiques, provoqués par le liquide contenant un ou plusieurs analytes dans le but de déterminer la concentration d'un analyte à surveiller ;

la première et la deuxième zone analytique représentant des surfaces d'un élément de test en continu, de préférence d'un ruban (108').

2. Système selon la revendication 1, dans lequel la mise en contact est mise en oeuvre en regroupant l'ouverture de sortie et la première et la deuxième zone analytique.

3. Système selon la revendication 1, dans lequel les zones analytiques sont mises en contact en retirant des portions du liquide hors du cathéter pour les amener sur la première et sur la deuxième zone analytique au moyen d'une unité d'éjection.

4. Système selon la revendication 1, dans lequel la première et la deuxième zone analytique représentent des objets séparés qui sont fixés à un support commun.

5. Système selon la revendication 1, dans lequel on applique une pression négative sur l'ouverture de sortie dans le but de transporter du liquide.

6. Système selon la revendication 1 ou 5, dans lequel le cathéter est conçu de telle sorte que du liquide ne sort pas de l'ouverture de sortie en l'absence de l'application d'une pression négative sur l'ouverture de sortie.

7. Système selon la revendication 1, 5 ou 6, dans lequel le regroupement de la zone analytique et de l'ouverture de sortie est synchronisé avec l'application d'une pression négative de telle sorte que du liquide qui sort de l'ouverture de sortie est récupéré par la zone analytique.

8. Système selon la revendication 1, dans lequel ledit dispositif analytique ou un dispositif d'application/détection supplémentaire détecte la présence de liquide ou la présence d'une quantité adéquate de liquide dans ou sur une zone analytique et interrompt la poursuite de la mise en contact de la zone analytique avec le liquide.

9. Système selon la revendication 5, dans lequel ledit dispositif analytique ou un dispositif d'application/détection supplémentaire détecte la présence de liquide ou la présence d'une quantité adéquate de liquide dans ou sur une zone analytique et interrompt l'application de la pression négative sur l'ouverture de sortie.

10. Système selon la revendication 1, comprenant un dispositif de contrôle qui synchronise le regroupement des première et deuxième zones analytiques

avec l'ouverture de sortie.

11. Système selon la revendication 1, 8 ou 9, dans lequel la quantité de liquide récupérée par une zone analytique est essentiellement égale ou supérieure au volume interne actif du cathéter.

12. Système selon la revendication 1, dans lequel le cathéter est conçu pour rester implanté entre les mises en contact avec la première et avec la deuxième zone analytique.

13. Système selon la revendication 1, dans lequel le système comprend une unité de transport pour le transport du système sur le corps et un magasin dans lequel les zones analytiques sont disposées et qui est conçu pour venir s'insérer dans l'unité de transport.

14. Système selon la revendication 1, dans lequel la quantité de liquide récupérée par une zone analytique est inférieure à 100 nl et se situe de préférence dans la plage entre 10 et 50 nl.

15. Système selon la revendication 1, dans lequel le dispositif analytique est conçu pour une analyse optique de zones analytiques.

16. Procédé pour surveiller la concentration d'analytes dans des liquides organiques, en particulier dans le liquide interstitiel, comprenant les étapes

- de la procuration d'une première et d'une deuxième zone analytique ;
- du regroupement de la première zone analytique avec une ouverture de sortie d'un cathéter implanté à des fins de mise en contact de la première zone analytique avec un liquide, ladite première et ladite deuxième zone analytique étant jetables de telle sorte qu'une zone analytique qui a été utilisée une fois n'est plus réutilisée ;
- de l'analyse du changement provoqué par le liquide contenant un ou plusieurs analytes dans la zone analytique dans le but de déterminer la concentration d'un analyte à surveiller ;

la première et la deuxième zone analytique représentant des surfaces d'un élément de test en continu, de préférence d'un ruban (108').

17. Procédé selon la revendication 16, dans lequel, après la mise en contact de la première zone analytique avec le liquide, la deuxième zone analytique et l'ouverture de sortie sont regroupées et mises en contact avec le liquide, et un changement dans la deuxième zone analytique, provoqué par le liquide contenant un ou plusieurs analytes, est analysé dans le but de déterminer la concentration d'un analyte à surveiller.

18. Procédé selon la revendication 16 ou 17, dans lequel la zone analytique est déplacée à la main en direction de l'ouverture de sortie.

19. Procédé selon la revendication 16 ou 17, dans lequel la zone analytique et l'ouverture de sortie sont regroupées au moyen d'un dispositif.

20. Nécessaire pour surveiller la concentration d'analytes dans des liquides organiques, en particulier dans le liquide interstitiel, comprenant :

- une unité de transport avec un cathéter comprenant une région implantable et une ouverture de sortie pour le retrait d'un liquide, en particulier d'un liquide organique ;
- deux zones analytiques ou plus pour la mise en contact avec le liquide, qui subissent un changement détectable lorsqu'un analyte est présent dans le liquide, lesdites première et deuxième zone analytique étant jetables, de telle sorte qu'une zone analytique qui a été utilisée une fois n'est plus réutilisée ;
- un dispositif analytique situé dans l'unité de transport ou présent séparément pour analyser les changements provoqués par le liquide contenant un ou plusieurs analytes sur les deux zones analytiques ou plus dans le but de déterminer la concentration d'un analyte à surveiller,

la première et la deuxième zone analytique représentant des surfaces d'un élément de test en continu, de préférence d'un ruban (108').

21. Nécessaire selon la revendication 20, possédant un dispositif pour regrouper une première zone analytique avec l'ouverture de sortie à des fins de mise en contact de la première zone analytique avec un liquide et pour le regroupement ultérieur de la deuxième zone analytique avec l'ouverture de sortie à des fins de mise en contact de la deuxième zone analytique avec un liquide.

22. Magasin pour des zones analytiques, qui possède

- une ouverture d'entrée pour un liquide ;
- au moins une première et une deuxième zone analytique qui, après la mise en contact avec un liquide organique subissent un changement détectable lorsqu'un analyte est présent dans le liquide organique, lesdites première et deuxième zone analytique étant jetables, de telle sorte qu'une zone analytique qui a été utilisée une fois n'est plus réutilisée ; et
- un dispositif pour amener la première et la

deuxième zone analytique à proximité de l'ouverture d'entrée de telle sorte que du liquide pénétrant dans le magasin entre en contact avec la zone analytique respective ;

la première et la deuxième zone analytique représentant des surfaces d'un élément de test en continu, de préférence d'un ruban (108').

23. Magasin selon la revendication 22, qui est fermé de telle sorte que l'on peut générer une pression négative dans le magasin en aspirant de l'air à l'extérieur du magasin.

24. Magasin selon la revendication 22 ou 23, qui possède une fenêtre optique.

25. Magasin selon la revendication 22, qui possède une liaison par fluide à un cathéter pour retirer un liquide d'un corps.

Fig. 1B

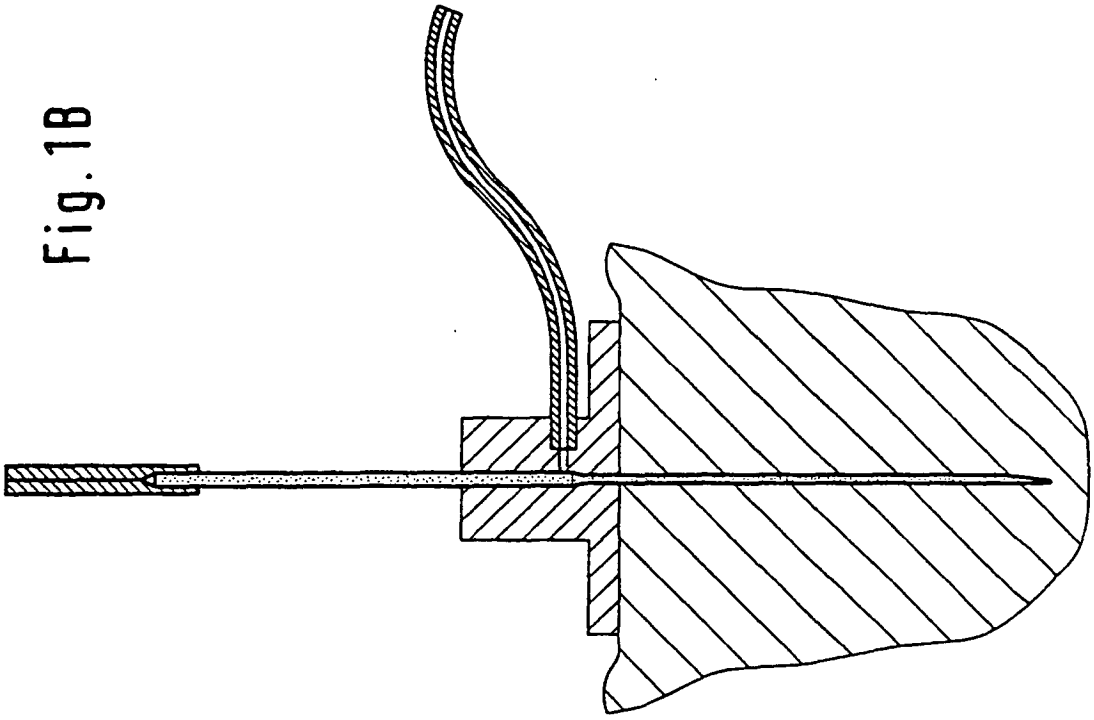


Fig. 1A

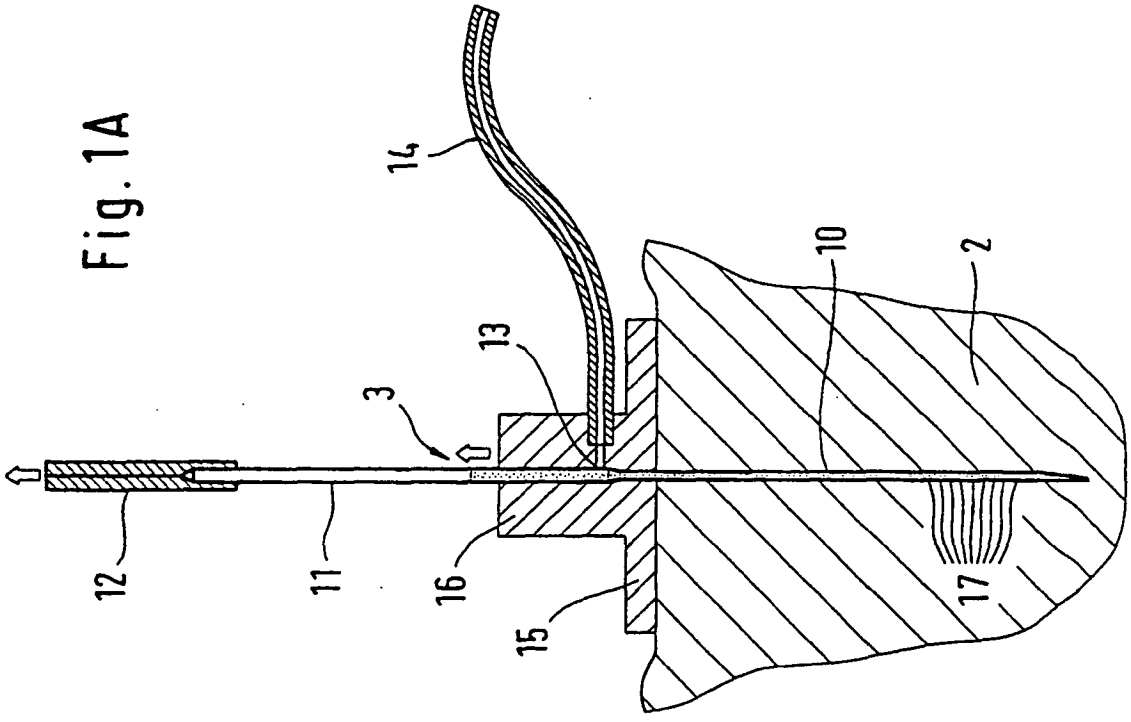


Fig.1D

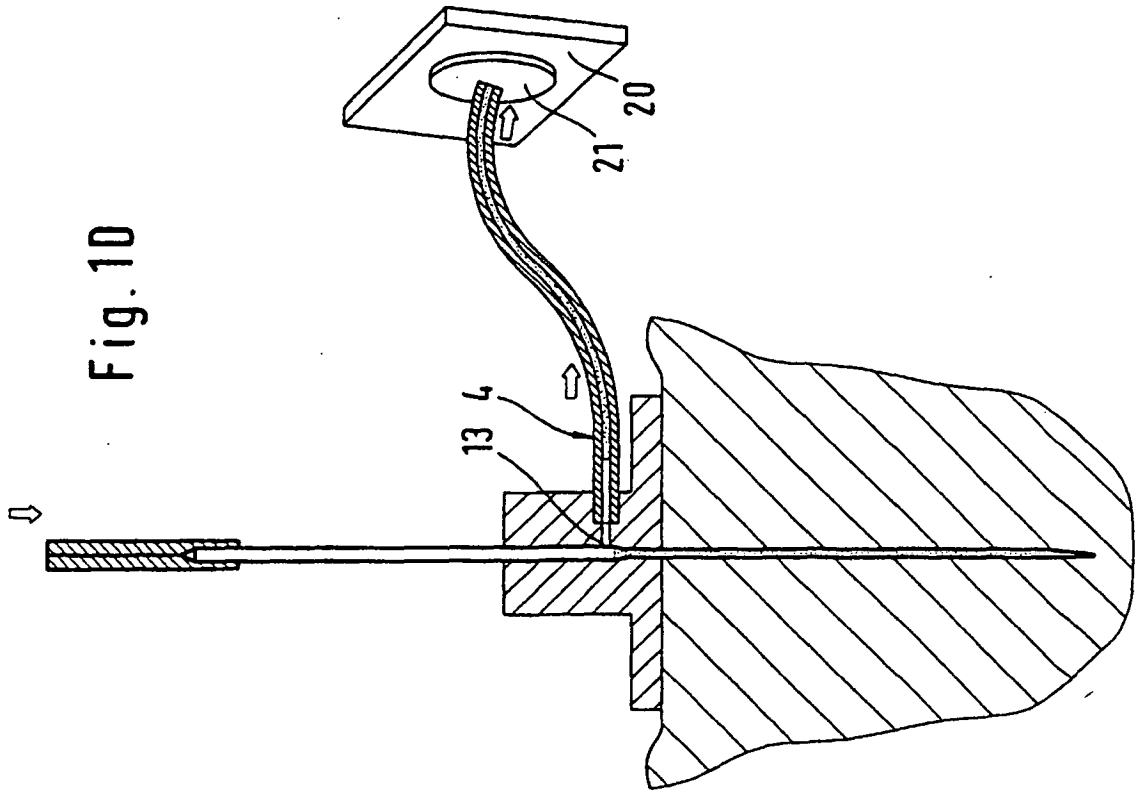


Fig.1C

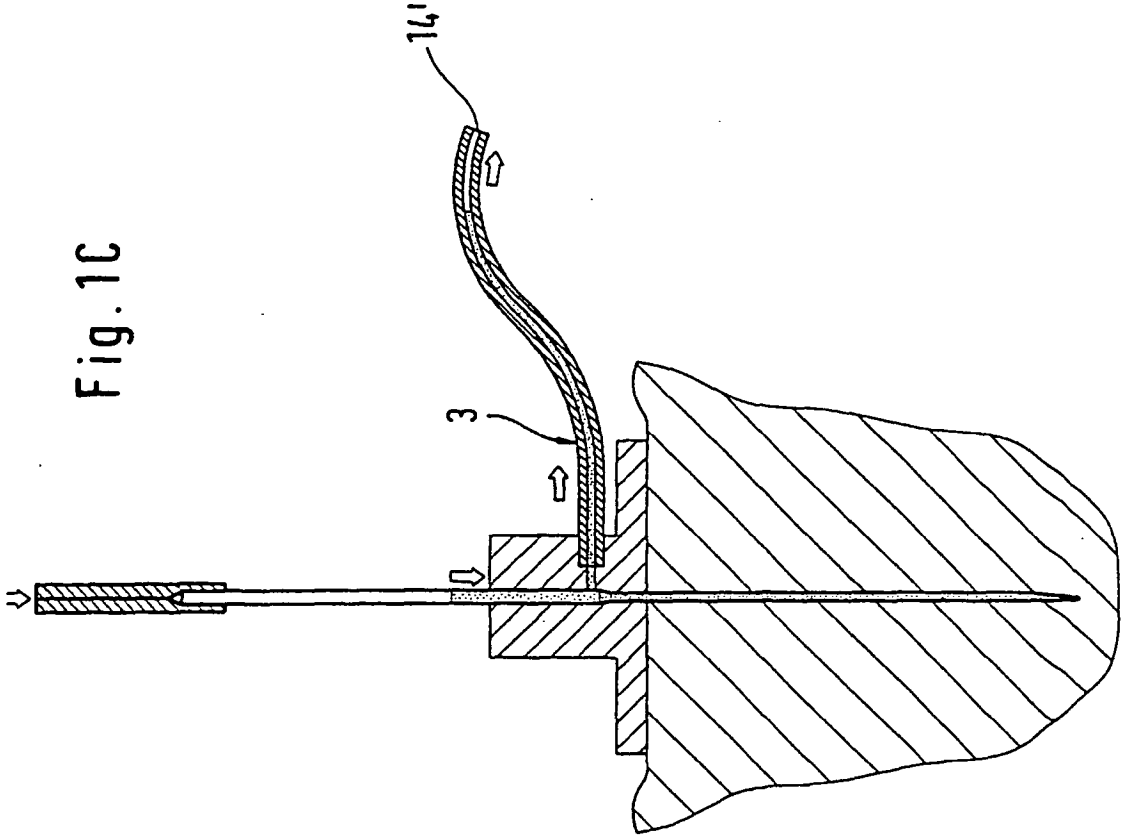
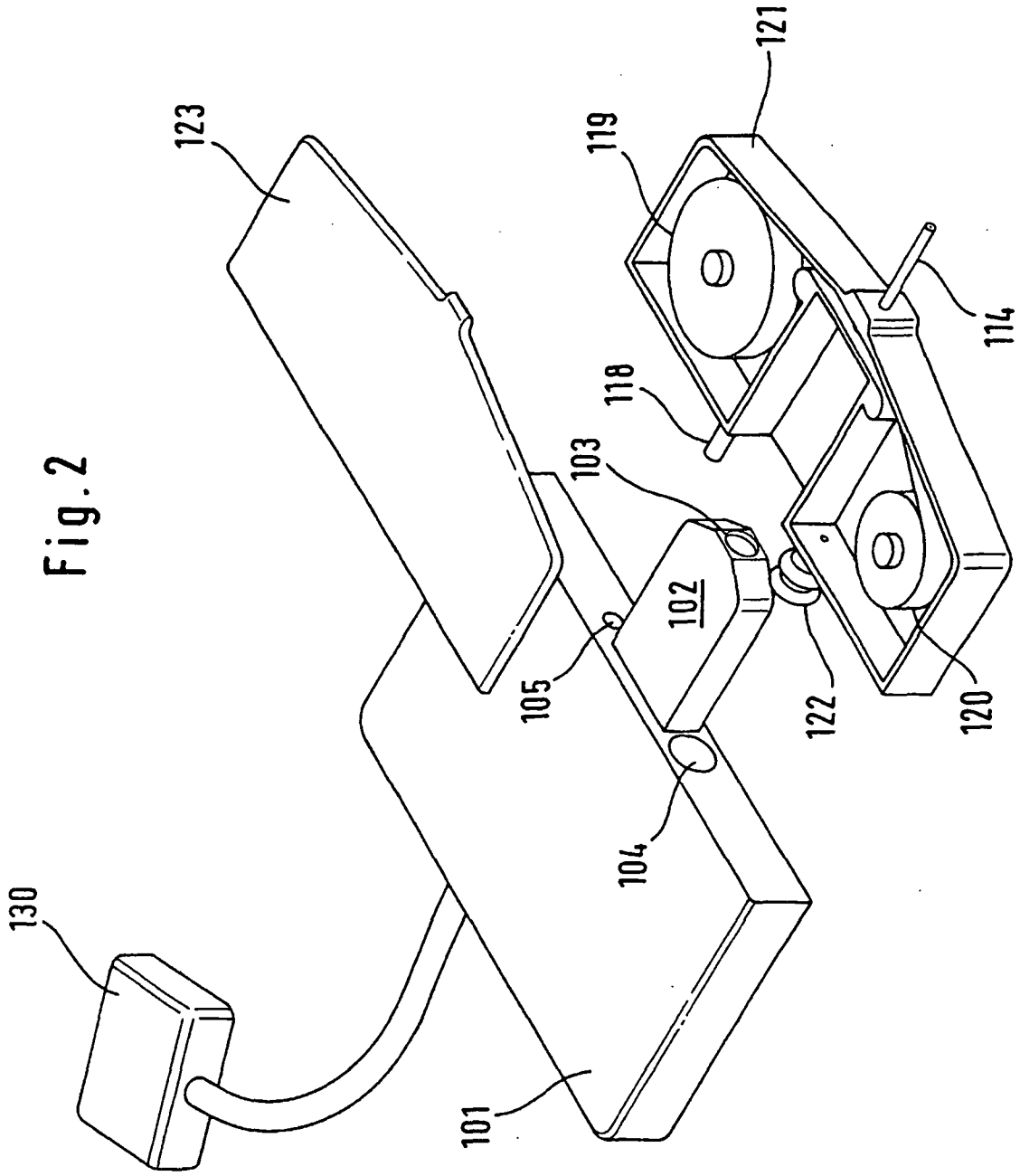


Fig. 2



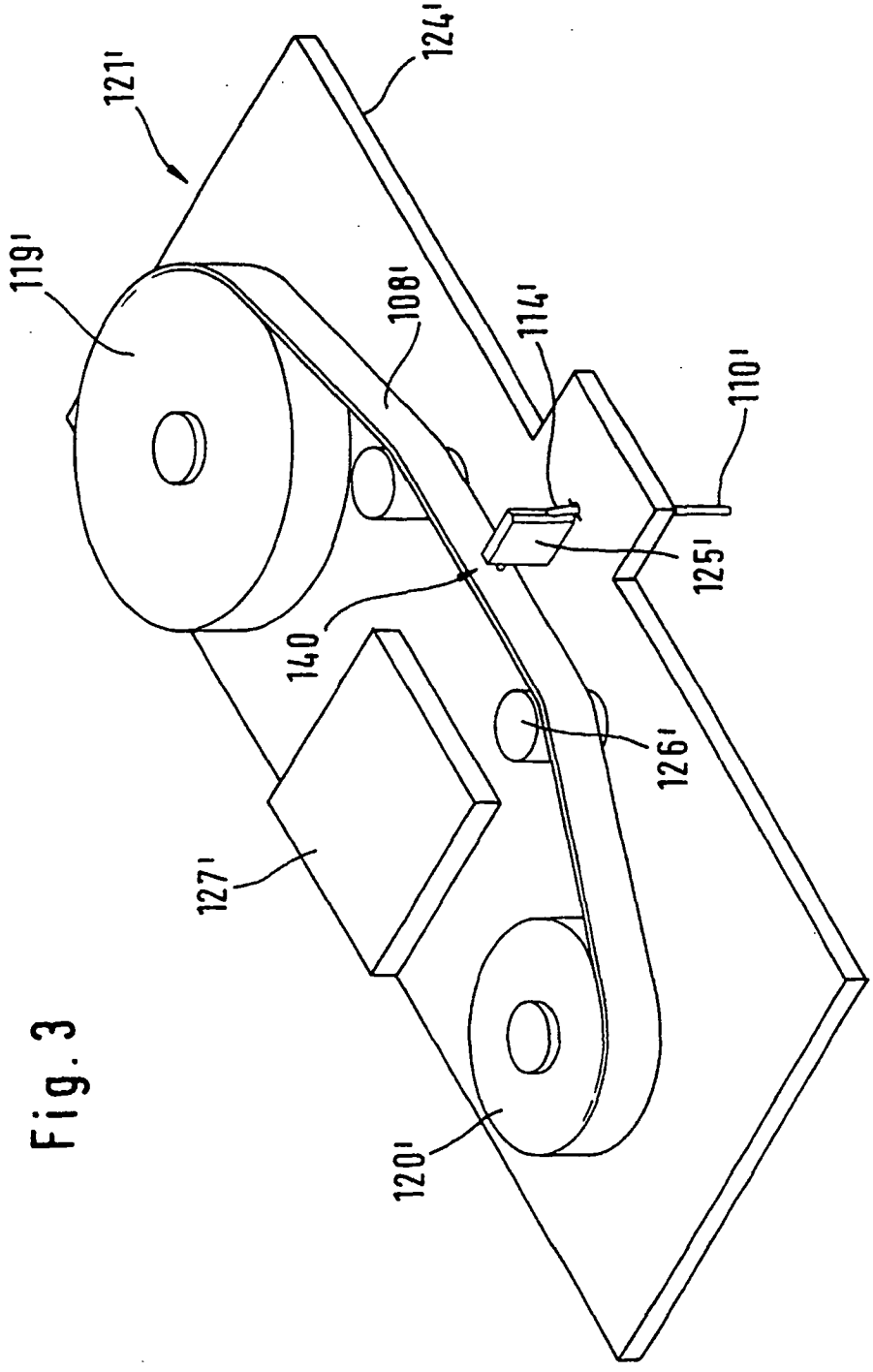
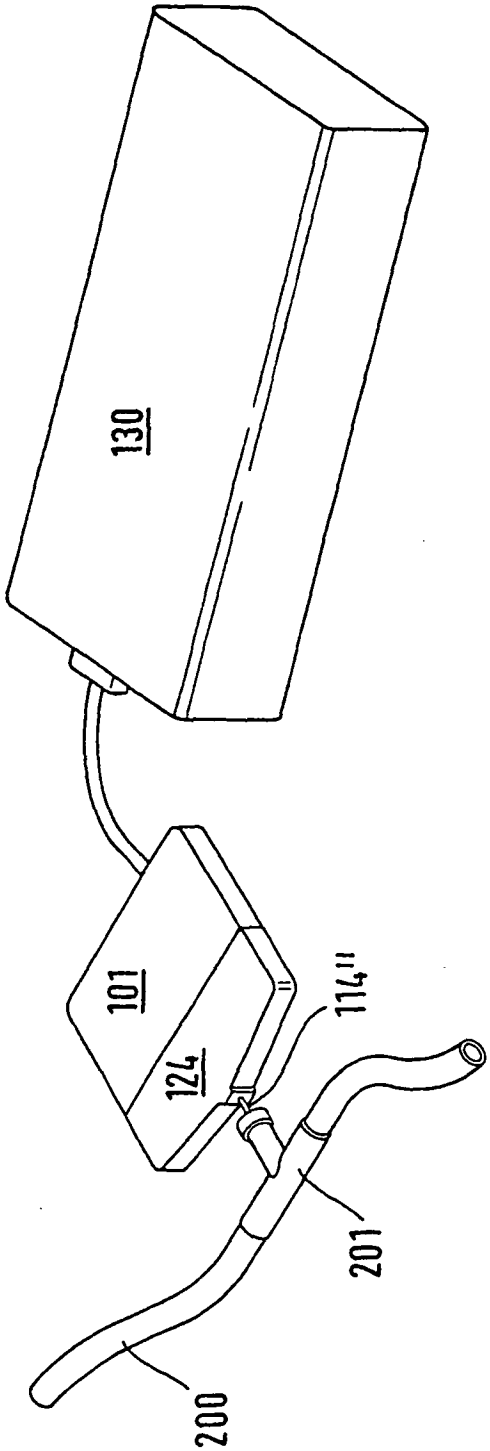


Fig. 3

Fig. 4



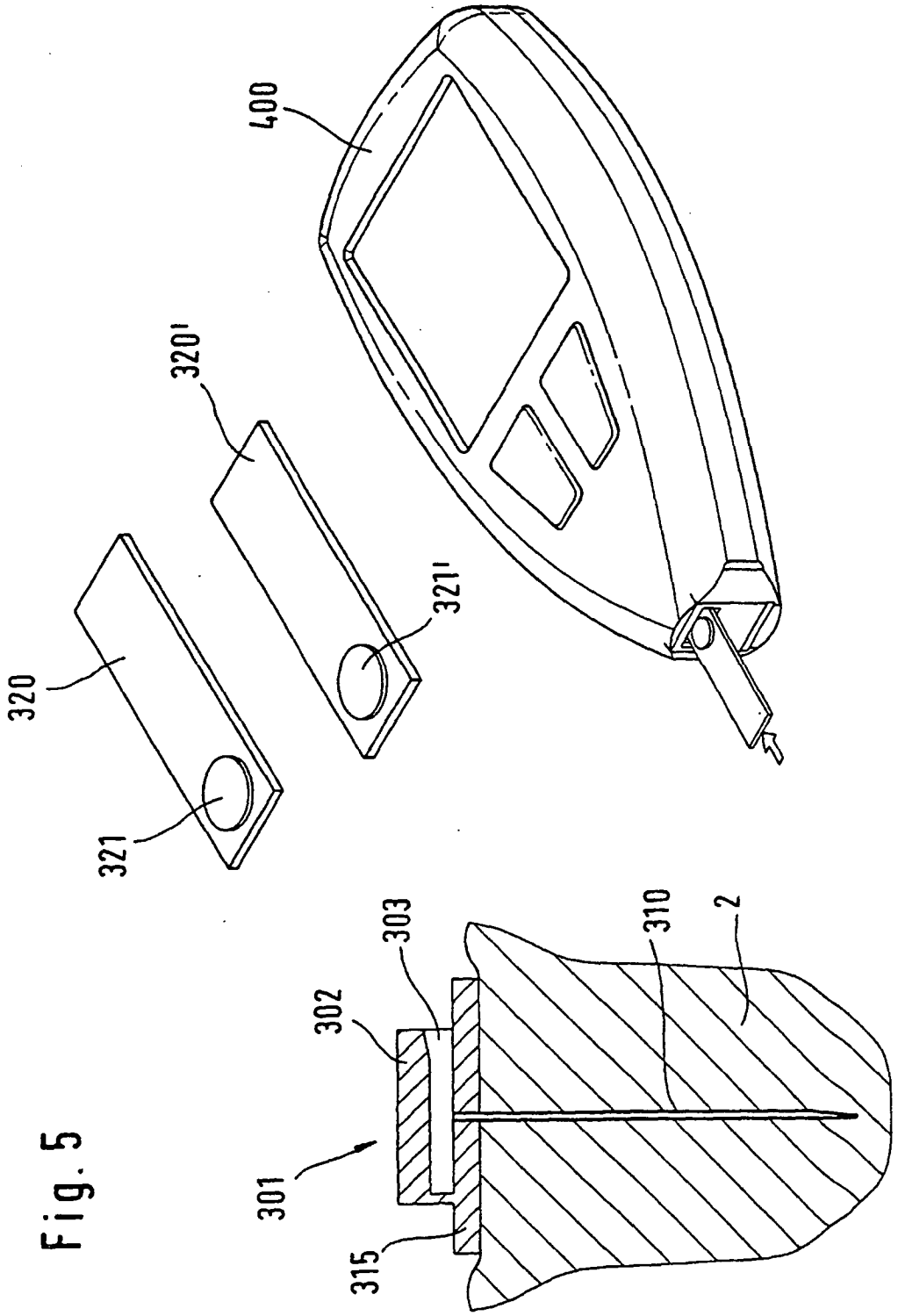


Fig. 5

REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	用于监测体液中分析物浓度的系统		
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其他公开文献	EP1359841A1		
外部链接	Espacenet		

摘要(译)

本发明涉及一种用于监测体液中，特别是间质液中的分析物浓度的系统，并且包括具有可植入区域和用于抽出流体特别是体液的出口的导管。第一和第二分析区与来自导管的流体顺序接触，并在存在分析物时经历可检测的变化。分析区可以用流体手动接触，并且还优选借助于装置以自动方式接触。根据本发明的系统另外具有分析装置，用于分析分析区域，以便基于分析物引起的变化确定分析物的浓度。本发明的另一主题是用于根据本发明的系统的导管以及包含测试区的杂志。