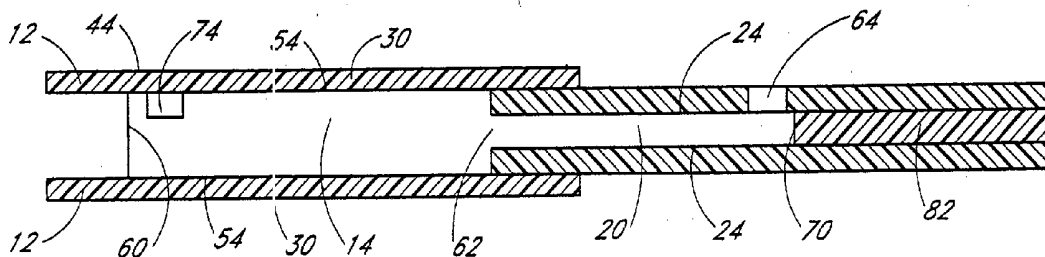




US 20040236250A1

(19) **United States**(12) **Patent Application Publication****Hodges et al.**(10) **Pub. No.: US 2004/0236250 A1**(43) **Pub. Date: Nov. 25, 2004**(54) **METHOD AND DEVICE FOR SAMPLING
AND ANALYZING INTERSTITIAL FLUID
AND WHOLE BLOOD SAMPLES**No. 09/536,235, filed on Mar. 27, 2000, now Pat. No.
6,612,111.(76) **Inventors: Alastair Hodges, San Diego, CA (US);
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Garry Chambers, San Diego, CA (US)****Publication Classification**(51) **Int. Cl.⁷ A61B 5/00**(52) **U.S. Cl. 600/583; 600/584; 73/864.01;
600/345**Correspondence Address:
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New Brunswick, NJ 08903 (US)**(57) **ABSTRACT**(21) **Appl. No.: 10/369,120**(22) **Filed: Feb. 13, 2003****Related U.S. Application Data**(63) **Continuation of application No. 10/166,487, filed on
Jun. 10, 2002, which is a continuation of application**

The invention disclosed in this application is a method and device for combining the sampling and analyzing of sub-dermal fluid samples, e.g., interstitial fluid or whole blood, in a device suitable for hospital bedside and home use. It is applicable to any analyte that exists in a usefully representative concentration in the fluid, and is especially suited to the monitoring of glucose.



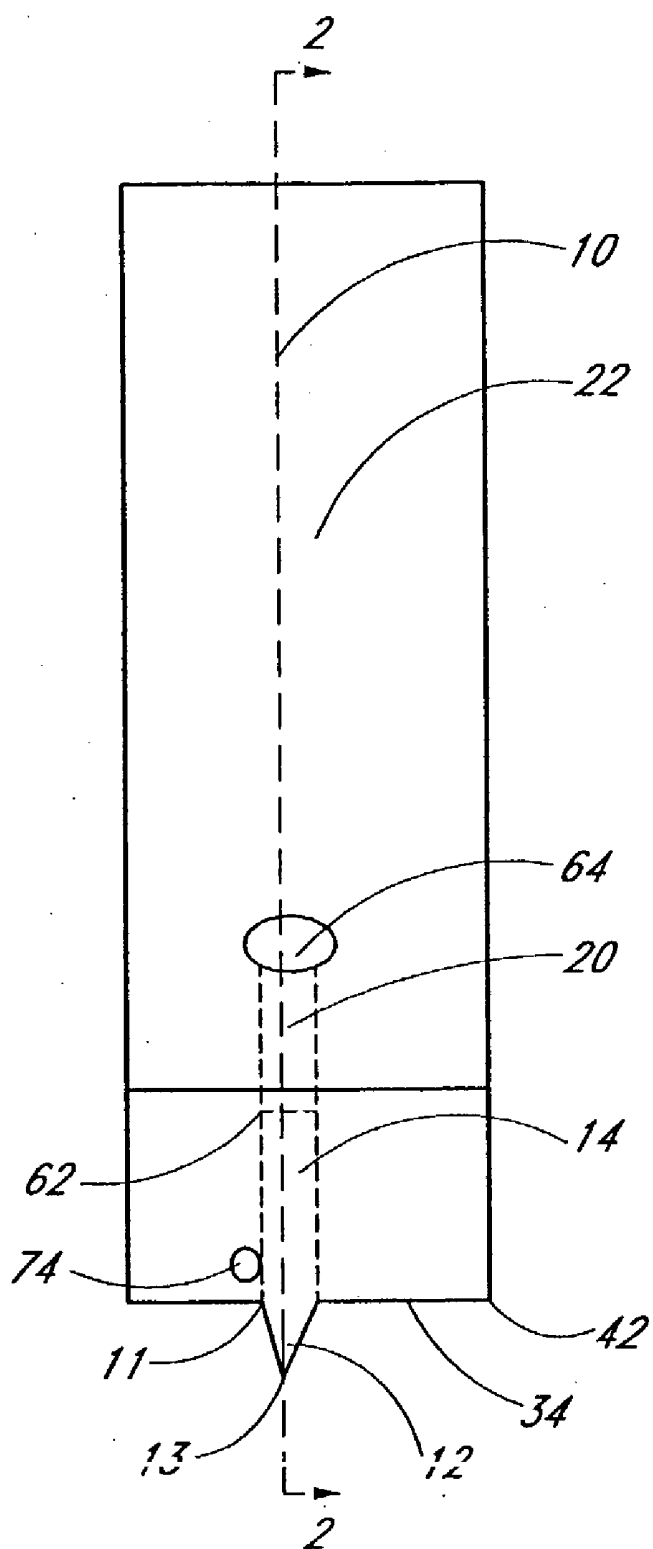


FIG. 1

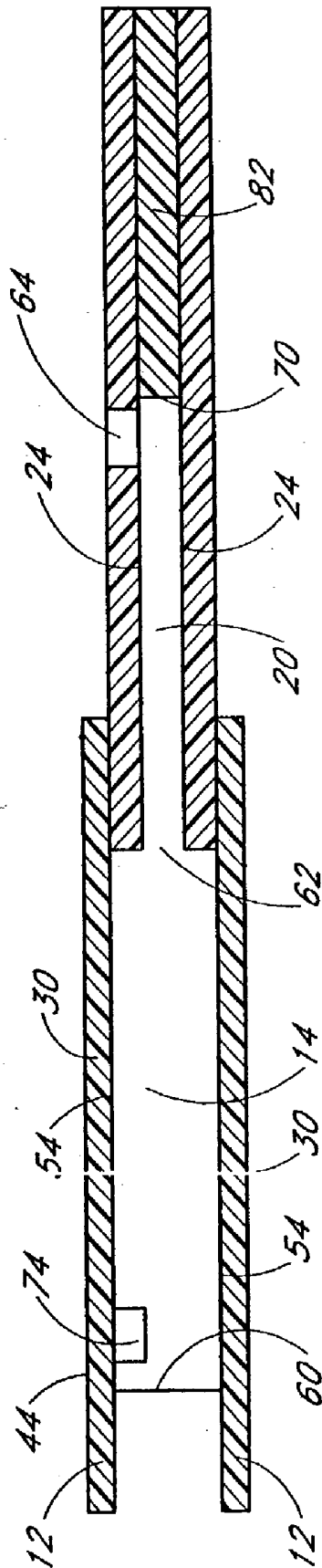


FIG. 2

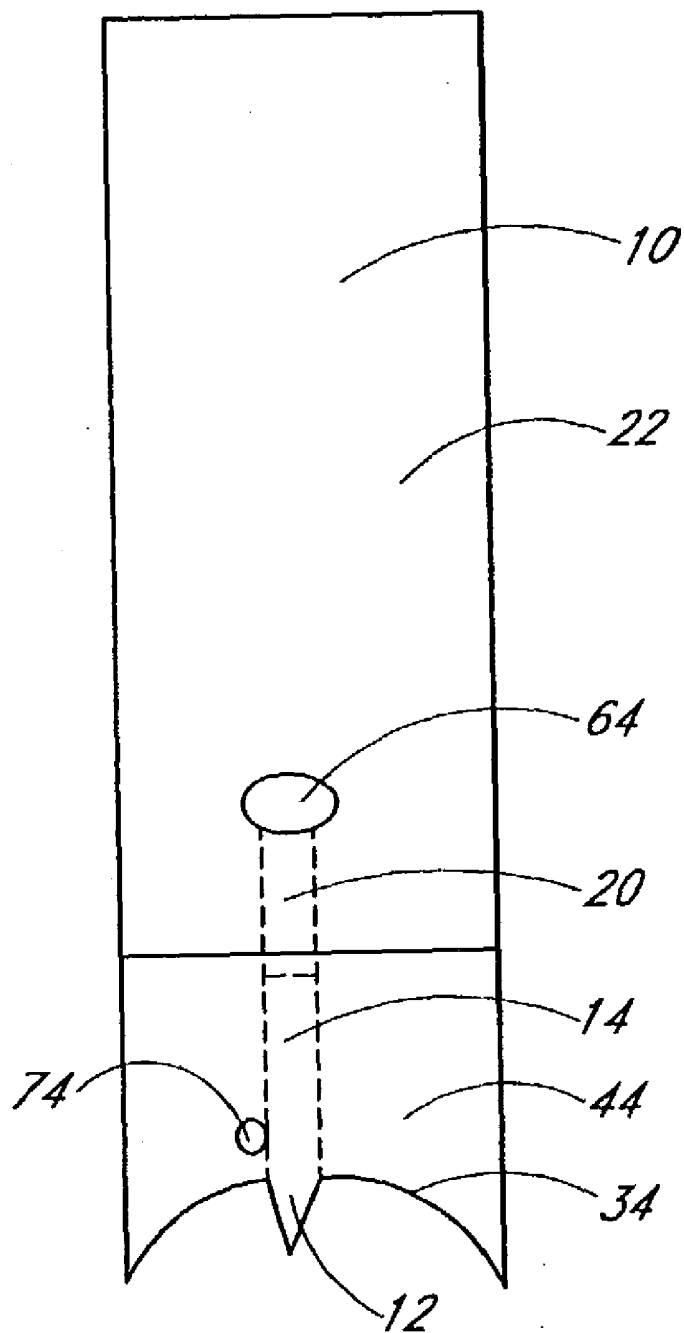


FIG. 3

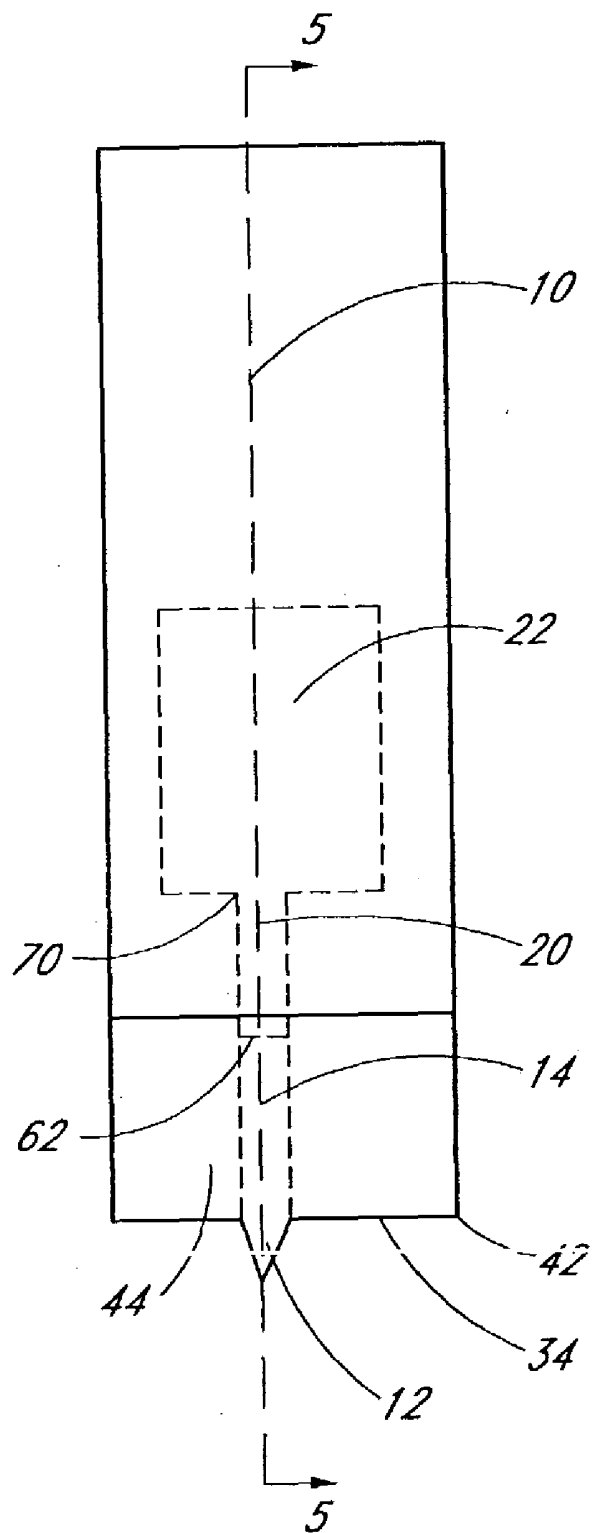


FIG. 4

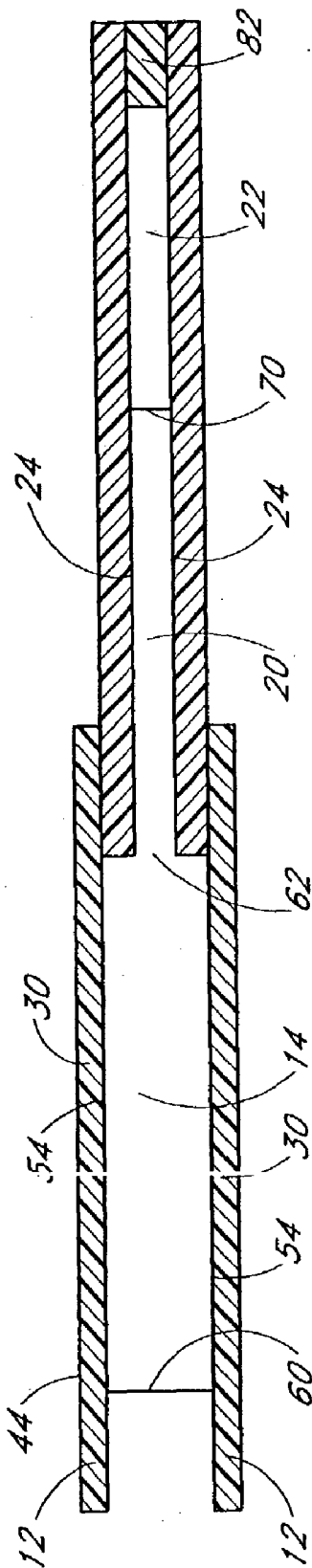


FIG. 5

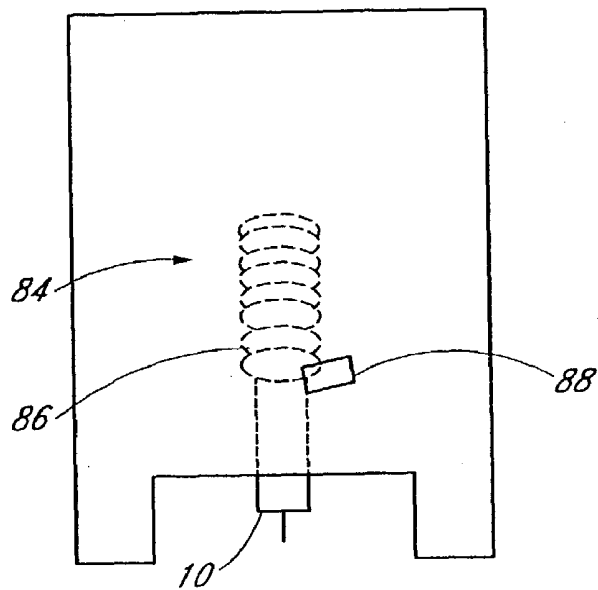


FIG. 6A

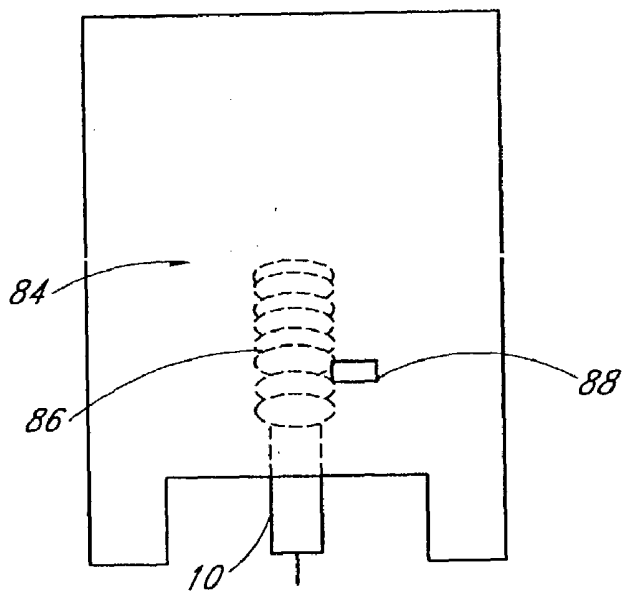
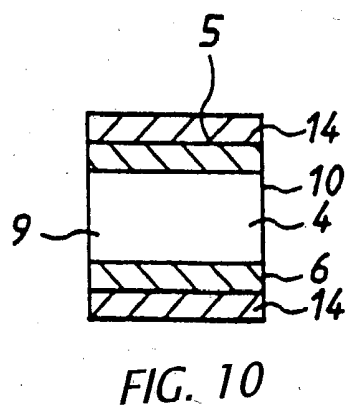
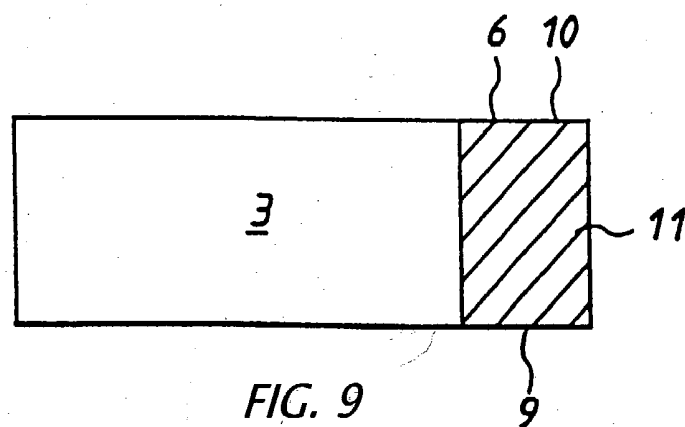
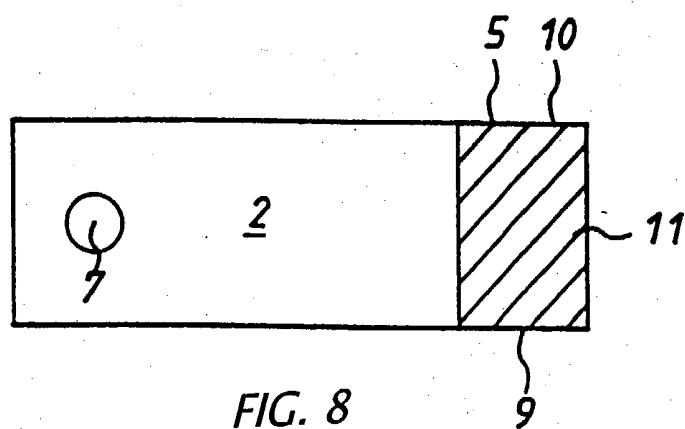
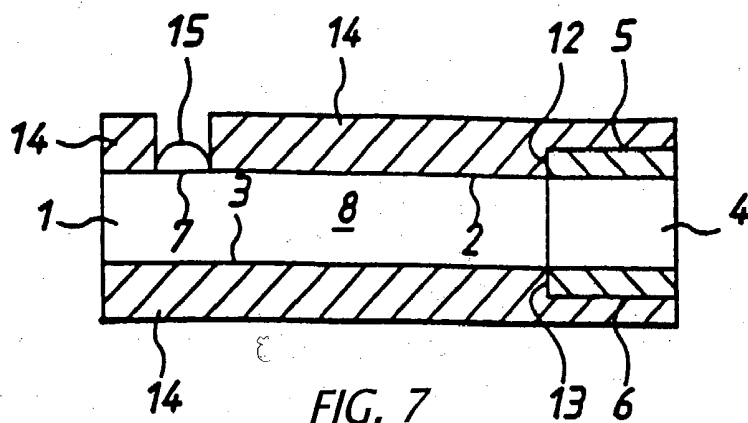
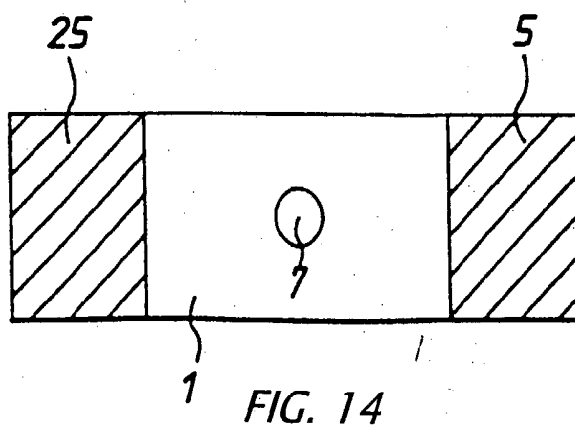
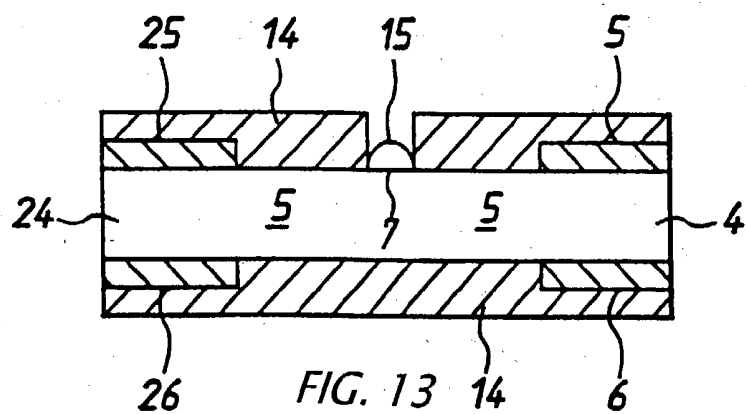
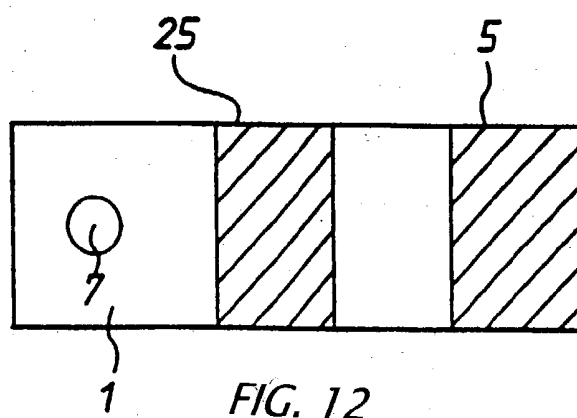
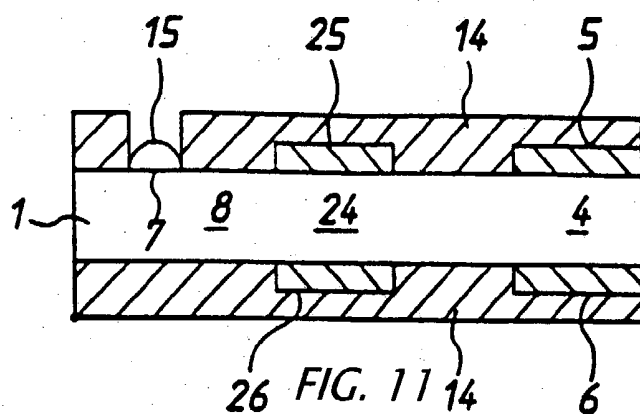


FIG. 6B





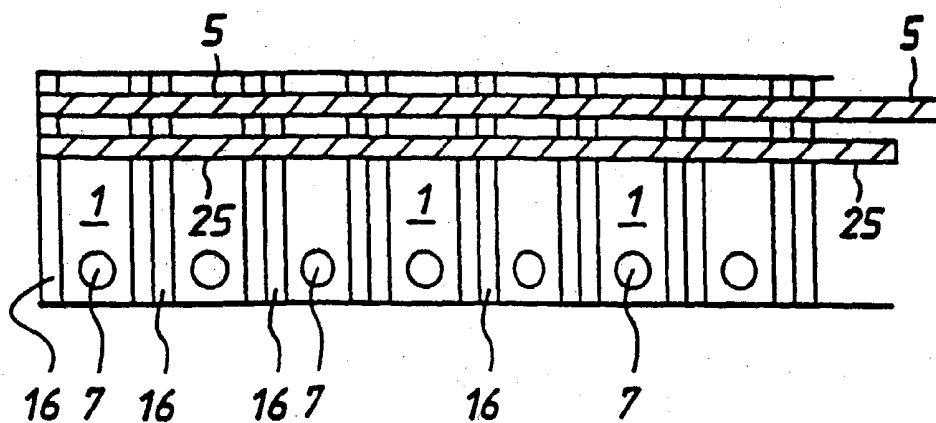


FIG. 15

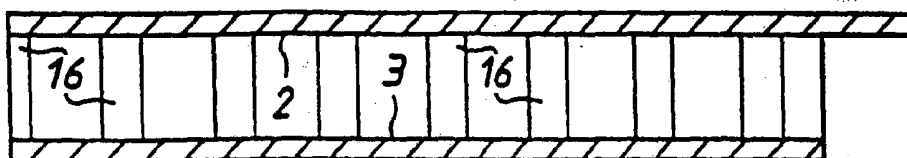


FIG. 16

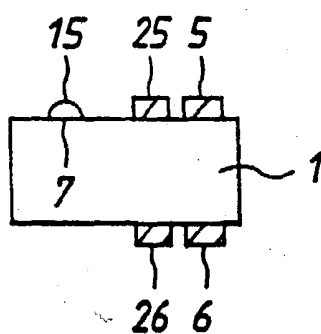


FIG. 17

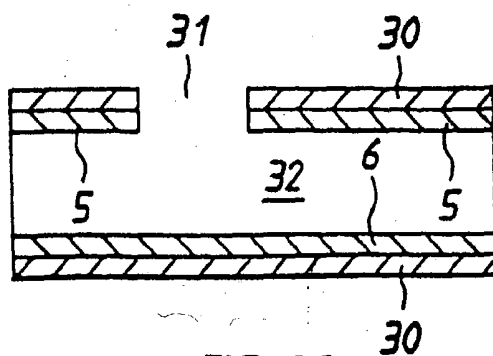


FIG. 18

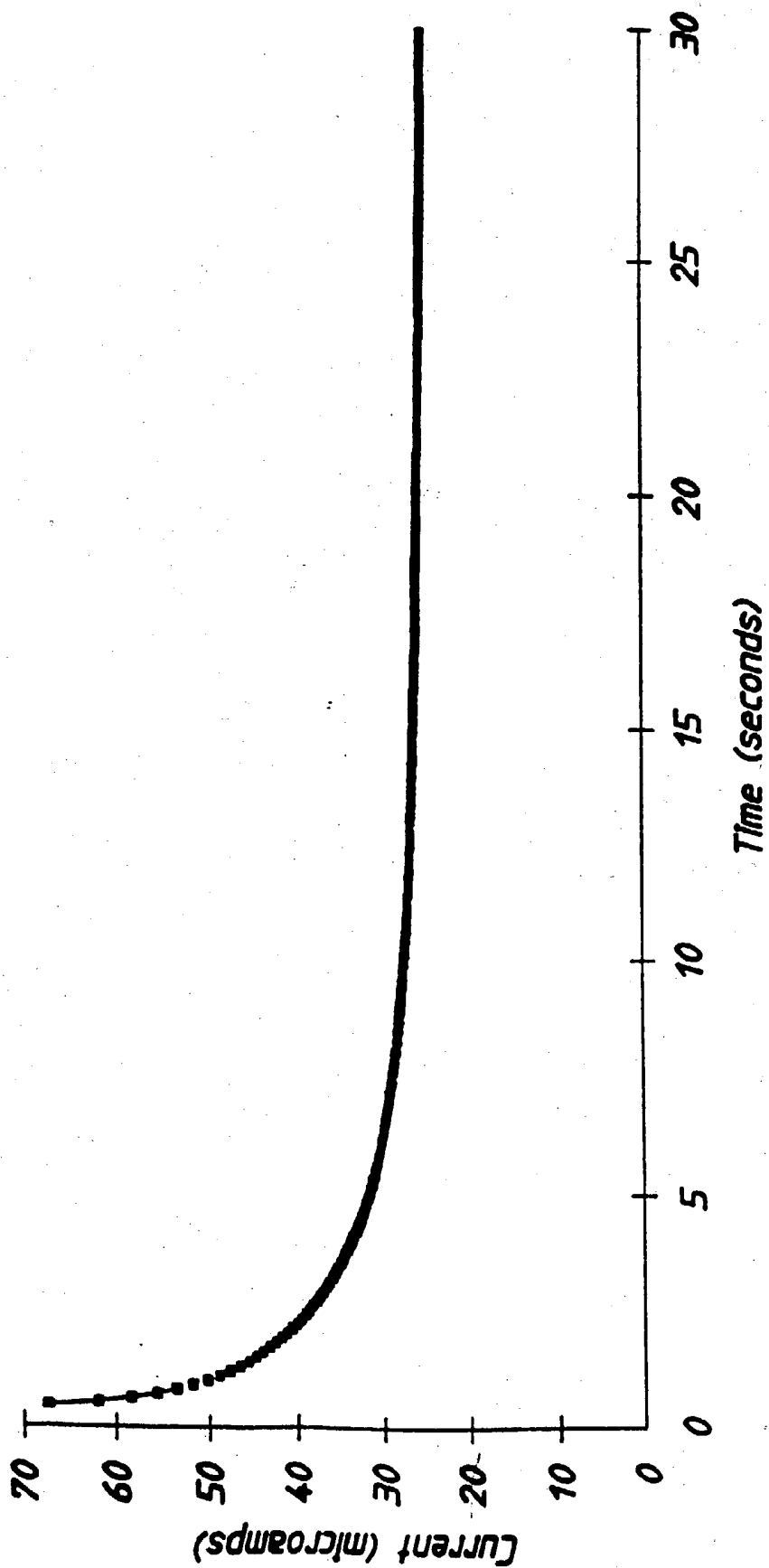


FIG. 19

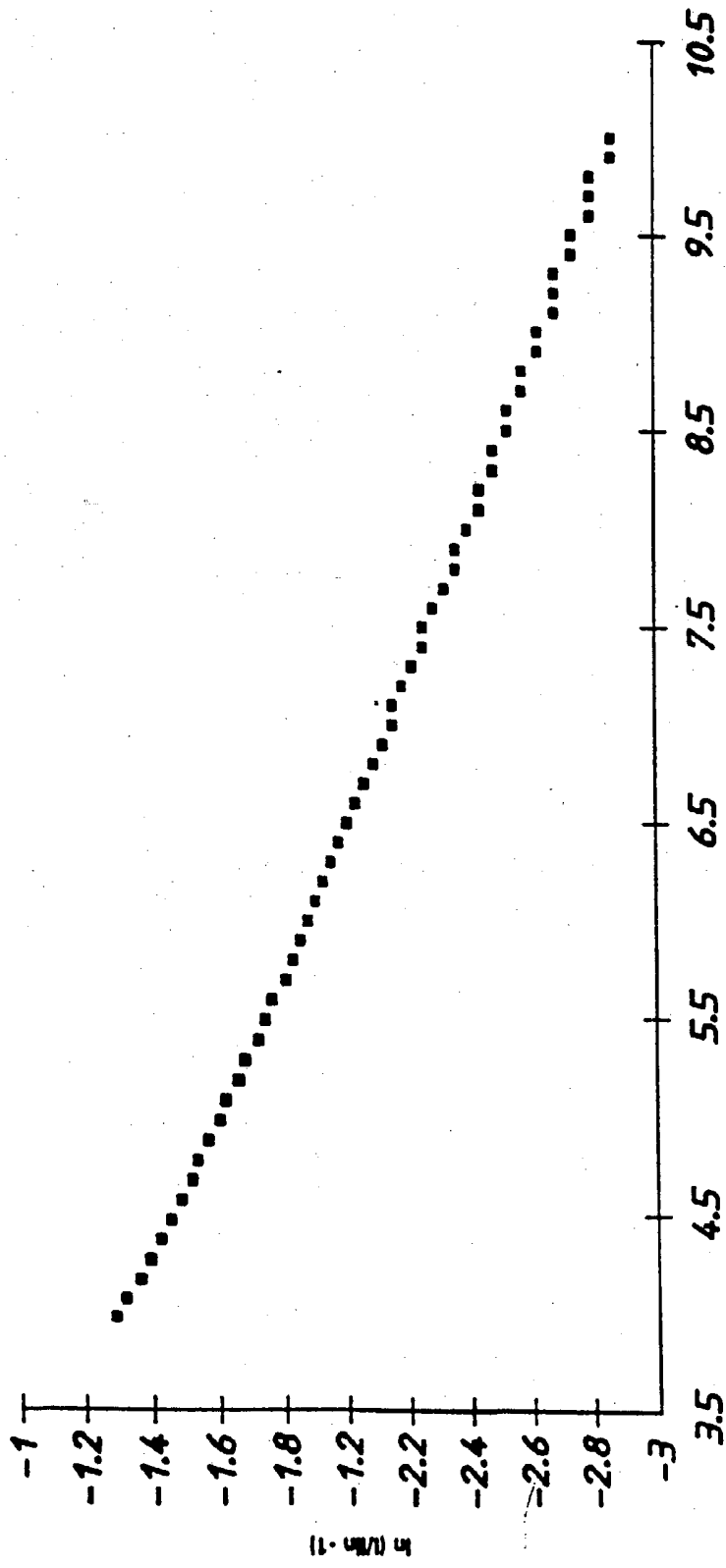


FIG. 20

METHOD AND DEVICE FOR SAMPLING AND ANALYZING INTERSTITIAL FLUID AND WHOLE BLOOD SAMPLES

RELATED APPLICATIONS

[0001] This application is a continuation of Application No. 10/166,487, filed Jun. 10, 2002, which is a continuation of Application No. 09/536,235, filed Mar. 27, 2000.

FIELD OF THE INVENTION

[0002] The present invention relates to a method and device for combining the sampling and analyzing of interstitial fluid or whole blood samples which is suitable for hospital bedside and home use.

BACKGROUND OF THE INVENTION

[0003] The management of many medical conditions requires the measurement and monitoring of a variety of analytes in bodily fluid. Historically, the measurement of analytes in blood has required an invasive technique, such as a venipuncture or finger puncture, to obtain blood for sampling purposes. An example of an analyte which is routinely tested by obtaining a blood sample through an invasive technique is glucose. In order to control their condition, diabetics must monitor their glucose levels on a regular basis. Invasive techniques used to obtain a blood sample for analysis have the disadvantage of being painful, which can reduce patient compliance in regular monitoring. Repeated testing, e.g., on a fingertip, can result in scar tissue build-up which makes obtaining a sample in that region more difficult. Moreover, invasive sampling procedures pose a risk of infection or disease transmission.

[0004] An alternative is to sample interstitial fluid rather than whole blood. Interstitial fluid is the fluid that fills the space between the connective tissue and cells of the dermal layer of the skin. An application where interstitial fluid has been shown to be an appropriate sampling substitute for plasma or whole blood is in the measurement of glucose concentration (J. Lab. Clin. Med. 1997, 130, 436-41).

[0005] In the patents U.S. Pat. No. 5,879,367, U.S. Pat. No. 5,879,310, U.S. Pat. No. 5,820,570 and U.S. Pat. No. 5,582,184 are disclosed methods of sampling using a fine needle in conjunction with a device to limit the penetration depth to obtain small volumes of interstitial fluid for the purpose of glucose monitoring. However, there is no method disclosed for analyzing the drawn samples that is suitable for home use or hospital bedside use.

SUMMARY OF THE INVENTION

[0006] It is desirable to be able to measure the concentration of analytes in humans or other animals without having to draw a blood sample by conventional methods. It is further desirable to be able to do so with an inexpensive disposable device that is simple enough for home or hospital bedside use.

[0007] The invention provides a suitable alternative to conventional sampling devices and methods that is less invasive than traditional whole blood sampling techniques and that requires a considerably smaller sample volume than is required in the conventional venipuncture or finger puncture sampling methods. Because of the smaller sample

volume required, a smaller wound is necessary to obtain the sample. In the conventional finger stick method, a drop of blood is formed on the tip of a finger, then the sensor sample entrance is wetted with the drop. Because the sample comes into contact with the skin surface, contamination of the sample by material on the skin surface is possible. The devices and methods disclosed herein do not require forming a blood drop on the surface of the skin, and therefore have less risk of sample contamination.

[0008] In one embodiment of the present invention, a fluid sampling device is provided which includes a body, the body including a dermal layer penetration probe having a penetrating end and a communicating end, and an analysis chamber having a proximal and distal end, the analysis chamber having a volume, wherein the penetration probe is in fluid communication with the analysis chamber such that fluid can flow from the penetration probe toward the analysis chamber. The analysis chamber can have at least one flexible wall which can be compressed to reduce the volume of the analysis chamber. The penetration probe can include, for example, a needle, a lancet, a tube, a channel, or a solid protrusion and can be constructed of a material such as carbon fiber, boron fiber, plastic, metal, glass, ceramic, a composite material, mixtures thereof, and combinations thereof. The penetration probe can include two sheets of material in substantial registration, having a protrusion on each sheet, wherein the sheets are spaced apart such that liquid can be drawn between the sheets by capillary action. The two sheets of material can extend into the device so as to form a pre-chamber. The penetration probe can be positioned within a recess in the proximal end of the device, and the recess can be configured to substantially align with a shape of a selected dermal surface.

[0009] In a further embodiment, the device can further include a pre-chamber having a volume and a first and second end, wherein the pre-chamber is interposed between the penetration probe and the analysis chamber such that the first end of the pre-chamber is adjacent the communicating end of the penetration probe and the second end of the pre-chamber is adjacent the proximal end of the analysis chamber. The volume of the pre-chamber can be greater than or equal to the volume of the analysis chamber. The pre-chamber can have at least one flexible wall that can be compressed to reduce the volume of the pre-chamber. The pre-chamber can also include a valve at the first end capable of substantially sealing the pre-chamber from the penetration probe.

[0010] In another embodiment, the device further includes a compressible bladder in communication with the analysis chamber, the compressible bladder being capable of applying a positive or a negative pressure to the analysis chamber.

[0011] In yet another embodiment, the pre-chamber and the analysis chamber can be capable of exerting different capillary forces. The capillary force exerted by the analysis chamber can be greater than the capillary force exerted by the pre-chamber. The differential capillary force can be derived, at least in part, from a difference between the pre-chamber height and the analysis chamber height. In this embodiment, the interior surface of the pre-chamber can include at least first and second pre-chamber walls spaced apart at a first distance to define a pre-chamber height, and the interior surface of the analysis chamber can include at

least first and second analysis chamber walls spaced apart at a second distance to define an analysis chamber height, wherein the height of the analysis chamber is less than the height of the pre-chamber.

[0012] In yet another further embodiment, at least one of the chambers can include a substance capable of enhancing or diminishing the capillary force exerted by the chamber. The substance can include, for example, a polymer, a resin, a powder, a mesh, a fibrous material, a crystalline material, or a porous material. Suitable substances include polyethylene glycol, polyvinylpyrrolidone, a surfactant, a hydrophilic block copolymer, and polyvinylacetate.

[0013] In a further embodiment, the device further includes a releasable actuator capable of supplying a force sufficient to cause the penetration probe to penetrate a dermal layer. The actuator can be external to or integral with the body, and upon release propels the body toward the dermal layer.

[0014] In a further embodiment, the analysis chamber can include an electrochemical cell including a working electrode and a counter/reference electrode and an interface for communication with a meter, wherein the interface communicates a voltage or a current.

[0015] In yet another embodiment of the present invention, a method for determining a presence or an absence of an analyte in a fluid sample is provided including the steps of providing a fluid sampling device as described above; penetrating a dermal layer with the penetration probe; substantially filling the analysis chamber with a fluid sample by allowing the sample to flow from the penetration probe toward the analysis chamber; and detecting a presence or an absence of the analyte within the analysis chamber. The sample can include, for example, interstitial fluid and whole blood. A qualitative or quantitative measurement of a characteristic of the sample can be obtained in the detecting step. The characteristic of the sample can include, for example, a reaction product of the analyte, such as a color indicator, an electric current, an electric potential, an acid, a base, a reduced species, a precipitate, and a gas. The analyte can include, for example, an ion such as potassium, an element, a sugar, an alcohol such as ethanol, a hormone, a protein, an enzyme, a cofactor, a nucleic acid sequence, a lipid, a pharmaceutical, and a drug. Cholesterol and lactate are examples of substances that can be analyzed.

[0016] In a further embodiment, the flow of sample toward the analysis chamber can be driven by a driving force, e.g., capillary force or a pressure differential. Where the analysis chamber has a flexible wall, the wall can be compressed to reduce the volume of the analysis chamber prior to penetrating the dermal, then the compression released to form a partial vacuum in the analysis chamber. Where the fluid sampling device further includes a compressible bladder, the bladder can be compressed to reduce its volume, then after penetration of the dermal layer the compression can be released to form a partial vacuum in the compressible bladder and analysis chamber.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] FIG. 1 shows a top view (not to scale) of one embodiment of a sampling device illustrating an arrangement of the penetration probe, pre-chamber, and analysis chamber.

[0018] FIG. 2 shows a cross section (not to scale) along the line A-A' of FIG. 1.

[0019] FIG. 3 shows a top view (not to scale) of one embodiment of a sampling device illustrating an arrangement of the penetration probe, pre-chamber, and analysis chamber wherein the proximal edge of the device forms a recess.

[0020] FIG. 4 shows a top view (not to scale) of one embodiment of a sampling device illustrating an arrangement of the penetration probe, pre-chamber, and analysis chamber.

[0021] FIG. 5 shows a cross section (not to scale) along the line B-B' of FIG. 4.

[0022] FIGS. 6a and 6b (not to scale) depict an embodiment of the invention wherein the device is loaded in a releasable actuator to facilitate penetration of a dermal layer by the penetration probe. FIG. 6a depicts the device loaded in the actuator, wherein the actuator is in the cocked position, ready to be triggered. FIG. 6b depicts the device and actuator after triggering.

[0023] FIG. 7 is a schematic drawing (not to scale) of a first embodiment according to the invention shown in side elevation.

[0024] FIG. 8 shows the embodiment of FIG. 7 in plan, viewed from above.

[0025] FIG. 9 shows the embodiment of FIG. 7 in plan, viewed from below.

[0026] FIG. 10 shows the embodiment of FIG. 7 viewed in end elevation.

[0027] FIG. 11 is a schematic drawing (not to scale) of a second embodiment according to the invention in side elevation.

[0028] FIG. 12 shows the embodiment of FIG. 11 in plan, viewed from above.

[0029] FIG. 13 is a schematic drawing (not to scale) of a third embodiment according to the invention, in side elevation.

[0030] FIG. 14 shows the embodiment of FIG. 13 in plan, viewed from above.

[0031] FIG. 15 is a schematic drawing (not to scale) according to the invention in plan view, viewed from above.

[0032] FIG. 16 shows the embodiment of FIG. 15 in end elevation.

[0033] FIG. 17 shows the embodiment of FIG. 15 in side elevation.

[0034] FIG. 18 shows a schematic drawing (not to scale) of a hollow cell embodiment according to the invention, viewed in cross section.

[0035] FIG. 19 is a graph showing a plot of current (ordinate axis) versus time (co-ordinate axis) during conduct of a method according to the invention.

[0036] FIG. 20 is a further graph of use in explaining the method of the invention.

[0037] In FIGS. 11 to 12, components corresponding in function to components of the embodiment of FIGS. 7 to 10 are identified by identical numerals or indicia.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0038] Introduction

[0039] The following description and examples illustrate various embodiments of the present invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope. Accordingly, the description of a preferred embodiment should not be deemed to limit the scope of the present invention. Methods and devices for optimizing sampling of fluid samples are discussed further in copending U.S. patent application Ser. No. 09/536,234, filed on Mar. 27, 2000, entitled "METHOD OF PREVENTING SHORT SAMPLING OF A CAPILLARY OR WICKING FILL DEVICE," which is incorporated herein by reference in its entirety.

[0040] The invention disclosed in this application is a method and device for combining the sampling and analyzing of a fluid sample from sub-dermal tissue in a device suitable for hospital bedside and home use. The fluid sample can comprise, but is not limited to, interstitial fluid or whole blood samples obtained from an animal. Any fluid sample obtained from sub-dermal tissue of a plant or an animal can be sampled and analyzed, thus the invention has broad application in the fields of human medicine, veterinary medicine, and horticultural science. The device and method are applicable to any analyte that exists in a usefully representative concentration in the fluid sample. For clarity, the present disclosure will discuss the application to glucose monitoring. However, it is to be understood that the invention is not limited to the monitoring of glucose, and that other analytes, as discussed below, can also be measured.

[0041] The method utilizes an integrated sampling and analyzing device 10 incorporating a penetration probe 12 capable of penetrating a patient's dermal layers to extract an interstitial fluid or whole blood sample, and a method for transferring the sample from the penetration probe 12 to the analysis chamber 20. In one embodiment, the device 12 can be a one-shot disposable device which can be inserted into a meter which communicates with the analysis chamber 20 to perform the analysis of the sample and present and optionally store the result.

[0042] In the device 10, a penetration probe 12 for penetrating the subject's dermal layers to collect an interstitial fluid or whole blood sample is integrated with an analysis chamber 20. A property of sampling interstitial fluid is that it can take from several to tens of seconds to collect sufficient sample to analyze. This is often not desirable for an analysis chamber 20 wherein the analyte undergoes a reaction as part of the analysis process, as it can be difficult to obtain an accurate start time for the test as well as achieve an even reacting reagent distribution in the sample. In a second aspect of the current invention a method is disclosed for collecting the sample in a pre-chamber 14 and, when full, transferring the sample quickly to an analysis chamber 20.

[0043] In this disclosure, unless a different meaning is clear from the context of its usage, "proximal" refers to a

region or structure of the device situated toward or adjacent to the dermal surface to be penetrated, and "distal" refers to a region or structure of the device situated toward the opposite (non-proximal) end of the device. For example, the penetration probe 12 is at the proximal end of the device.

[0044] The Penetration Probe

[0045] The penetration probe 12 can be any device capable of penetrating the patient's dermal layers to the desired extent and capable of transporting a sample to a pre-chamber 14 or analysis chamber 20. The penetration probe 12 comprises two ends, as illustrated in FIG. 1. The penetrating end 11 of the penetration probe 12 is the end inserted into the dermal layer. The communicating end 13 of the penetration probe 12 is the end which is in communication with either the pre-chamber 14 or the analysis chamber 20.

[0046] One or more protrusions 12 with at least one sharp edge or point are suitable as the penetration probe 12. The penetration probe 12 can be fabricated from materials including plastic, metal, glass, ceramic, a composite material (e.g., a composite of ceramic and metal particles), or mixtures and combinations of these materials. The penetration probe 12 can be in the form of a solid protrusion, a needle, a lancet, a tube or a channel. The channel can optionally be open along one or more of its elongated sides. As illustrated in FIG. 2, a preferred embodiment of the penetration probe 12 is two sheets 30 of material formed so as to have a sharply pointed protrusion 12 on each sheet 30 in substantial registration, with the sheets 30 spaced apart such that liquid can be drawn between the sheets 30 by capillary action. In a particularly preferred embodiment, the two sheets 30 of material extend to and overlap with the analysis chamber 20 to form a pre-chamber 14 for sample collection.

[0047] When interstitial fluid is sampled, the penetration depth can be controlled by limiting the length the penetration probe 12 protrudes from the proximal surface 34 of the sampling device 10 to less than the thickness of the dermal layer. In a preferred embodiment, the length of the protrusion 12 will be less than 2 to 3 mm, more preferably about 1.5 mm. After penetration to a suitable depth corresponding to the length of the protrusion 12, contact between the surface of the dermal layer and the surface 34 of the analyzing device prevents further penetration. For other uses, such as in sampling interstitial fluid from regions having a thick dermal layer, or for veterinary uses, it can be desirable for the length of the protrusion 12 to be greater than 3 mm. Accordingly, the invention contemplates protrusions 12 of any length, wherein the length is sufficient to sample interstitial fluid. When whole blood is sampled, a slightly longer penetration probe 12 should be used, i.e., one having a length greater than 2 to 3 mm.

[0048] The diameter or width of the penetration probe 12 depends upon the design of the penetration probe 12. Suitable diameters or widths are those which provide sufficient sample flow. In the case of a protrusion 12 forming a sharp edge or point, or a tube or channel, the minimum diameter or width is typically greater than about 10 μm . When the penetrating means 12 comprises two sheets 30 in substantial registration, each having a sharply pointed protrusion 12, the two protrusions 12 are typically spaced from 1 mm to 10 μm apart.

[0049] The penetration probe 12 can be located on any suitable part of the test strip 10, i.e., an edge 34, a corner 42,

or one of the flat surfaces 44. Protection can be provided to the penetration probe 12 by locating it within a recess formed in the distal edge 34 of the test strip 10, as shown in FIG. 3, or in a depression on the surface 44 of the test strip 10. In a preferred embodiment, the recess in the distal edge 34 of the test strip 10 can be configured to substantially align with the shape of a selected dermal surface, e.g., a fingertip. However, the recess can be configured in other suitable shapes, e.g., a square recess, a V-shaped recess, a curved recess, a polygonal recess, and the like. In a preferred embodiment, the penetration probe 12 does not protrude past the proximal-most portion of the proximal edge 34 or surface 44 of the device 10, but when pressed against the skin, the skin deforms into the recess and is punctured by the penetration probe 12. Such an arrangement aids sampling by compressing the area of the skin around the sampling point. The penetration probe 12 can form an integral part of another component of the test strip 10, e.g., a side of the pre-chamber 54, as shown in FIG. 2. Alternatively, the penetration probe 12 can comprise a separate part which is attached to or incorporated into the test strip 10 by any suitable means, e.g., adhesive, thermal bonding, interlocking parts, pressure, and the like. The penetration probe 12 can be retractable or non-retractable.

[0050] Penetration itself can be accomplished by any suitable means, including inserting the penetration device 12 manually or by means of a releasable actuator 84 such as, for example, a spring-loaded mechanism 84 as depicted in FIGS. 6a and 6b. Such a spring-loaded mechanism 84 incorporates a spring 86 which is compressed and held in place by a trigger 88 which can release the force compressing the spring 86 when the triggering mechanism is activated. The trigger 88 can be activated manually, or the device 84 can incorporate a pressure sensor which indicates that sufficient pressure has been applied to obtain the sample, thereby activating the trigger 88. In one embodiment, the distal end of the device 10 is placed in the spring-loaded mechanism 84 such that when the force compressing the spring 86 is released by activating the trigger 88, force is transferred to the device 10, which is ejected from the mechanism 84, thereby inserting the penetrating probe 12 into the dermal layer.

[0051] Any suitable body part can be used for sampling. In a preferred embodiment, the sampling area is one which does not have a high density of nerve endings, e.g., the forearm. Typically, 5 to 15 seconds is required to obtain sufficient sample. Application of pressure to the sampling area can be needed to extract interstitial fluid or whole blood. To facilitate the appropriate amount of pressure being applied, a pressure sensor can be incorporated into the device 10 which indicates when sufficient pressure has been applied. Sample acquisition time can be improved by applying increased pressure to the area surrounding the direct sampling area. Some of the factors that can affect interstitial fluid or whole blood sample acquisition include the patient's age, skin thickness, temperature, and hydration. The amount of interstitial or whole blood sample collected for testing can preferably be about 0.02 μ l or greater, more preferably 0.1 μ l or greater, and most preferably about 0.5 μ l or greater.

[0052] In one preferred embodiment, the device 10 can be inserted into a meter prior to sample acquisition. In such an embodiment, the meter serves multiple functions, including

supporting the device 10, providing an automated means of initiating sample acquisition, and indicating when sample acquisition is complete.

[0053] Transfer of Sample from Penetration probe to Analysis Chamber

[0054] In a preferred embodiment of the sampling device 10, the device comprises two parts—the penetration probe 12 and an analysis chamber 20. In another preferred embodiment, illustrated in FIGS. 1 and 2, the device 10 comprises the penetration probe 12 and a pre-chamber 14. The pre-chamber 14 can then be integrated with or can be interfaced to the analysis chamber 20.

[0055] In a further embodiment, the analysis chamber 20 is integrated with or can be interfaced to a means for facilitating filling of the analysis chamber 20. This means can comprise a collapsible or compressible bladder 22, as shown in FIGS. 3 and 4, which can be used to apply a positive or negative pressure (i.e., partial vacuum) to the analysis chamber 20. The compressible bladder 22 can comprise any chamber with flexible walls that can be compressed to reduce the volume of the chamber. When the force compressing the compressible bladder 22 is released, a partial vacuum is formed which draws sample into the analysis chamber 20. In a preferred embodiment, the volume of the compressible bladder 22 is sufficiently large so that when the bladder 22 is substantially fully compressed, the reduction in volume of the bladder 22 is larger than or equal to the total volume of the analysis chamber 20, thereby ensuring that the analysis chamber 20 is substantially filled. However, a compressible bladder 22 with a smaller volume than the analysis chamber 20 can also be effective in assisting the filling of the analysis chamber 20.

[0056] Alternatively, the analysis chamber 20 itself can be collapsible or compressible. In such an embodiment, a piston or other compressing agent, such as a patient's or clinician's fingers, can first compress then release the analysis chamber 20, thereby forming a partial vacuum. When the compressing force is released, the partial vacuum causes the sample to flow from the penetration probe toward the analysis chamber.

[0057] Pre-chamber

[0058] In a preferred embodiment, as illustrated in FIGS. 1 and 2, a pre-chamber 14 is provided in the integrated sampling and testing device 10 for accumulation and storage of the collected sample prior to its being transferred to the analysis chamber 20. A pre-chamber 14 is useful when using an analysis method which requires that the sample fill the analysis chamber 20 in a short period of time to return accurate results, i.e., a time shorter than that required to draw sufficient sample from the dermal layer. In a preferred embodiment, the volume of the pre-chamber 14 is larger than that of the analysis chamber 20, thus ensuring that once the pre-chamber 14 is filled, sufficient sample has been collected to completely fill the analysis chamber 20.

[0059] In a preferred embodiment, as illustrated in FIGS. 1 and 2, the penetration probe 12 opens into the pre-chamber 14 at a first end, and at the second end the pre-chamber 14 opens to the analysis chamber 20. The pre-chamber 14 can be free of reagents or other substances, or can optionally contain one or more substances to enhance or diminish the capillary force exerted by the walls of the

pre-chamber 14 or to pre-treat the sample prior to analysis. These substances can include, for example, polymers, resins, powders, meshes, fibrous materials, crystalline materials, porous materials, or a mixture or combination thereof. To facilitate effective filling of the analysis chamber 20, a preferred embodiment utilizes a pre-chamber 14 and analysis chamber 20 of different heights, as shown in FIG. 2. Where the analysis chamber 20 is formed so that its height (typically referring to the smallest chamber dimension) is smaller than the height of the pre-chamber 14, a capillary force is generated that is capable of drawing fluid out of the pre-chamber 14 and into the analysis chamber 20. A first air vent 64 can be formed at the end 70 of the analysis chamber 20 opposite the opening 62 to the pre-chamber 14, facilitating the filling of the analysis chamber 20 by allowing air to be displaced from the analysis chamber 20 as sample enters. Optionally, a second vent 74 can be formed opening into the pre-chamber 14 at the substantially opposite end 60 of the pre-chamber 14 to where the penetration probe 12 opens into the pre-chamber 14. This vent 74 provides air to the pre-chamber 14 to replace the sample as it is transferred from the pre-chamber 14 to the analysis chamber 20. The vent 74 can be placed in any suitable position on the test strip 10. In a preferred embodiment, the vent 74 incorporates a sharp corner, e.g., at a 90° angle, which functions as a "capillary stop" to prevent sample from exiting the device 10 through the vent 74.

[0060] In another embodiment, the pre-chamber 14 consists of a tube, or other shaped chamber, with flexible walls, attached to the penetration probe 12. In this embodiment, the pre-chamber 14 is either permanently fixed to the analysis chamber 20 or is placed next to and aligned with a port to the analysis chamber 20. Such alignment can occur during use by suitable placement in an external device such as the measurement meter.

[0061] In one aspect of this embodiment, the pre-chamber 14 further comprises a valve, defined as a device to control the flow of fluid sample between the penetration probe 12 and the pre-chamber 14. The valve can comprise one or more rollers, pistons, or squeezing devices capable of simultaneously closing off the first end 60 of the pre-chamber 14, and compressing the pre-chamber 14 such that the fluid in the pre-chamber 14 is forced towards the second end 62 of the pre-chamber 14 and subsequently into the analysis chamber 20.

[0062] Alternatively, the analysis chamber 20 consists of a tube, or other shaped chamber, with flexible walls, attached to the penetration probe 12. In one aspect of this embodiment, the analysis chamber 20, prior to penetration, is compressed by one or more rollers, pistons, or other squeezing devices. After the penetration probe 12 is inserted, the compression is released, forming a vacuum which pulls sample into the analysis chamber 20. In such an embodiment, the pre-chamber 14 can not be necessary if sufficient vacuum is generated for rapid sample acquisition. In such an embodiment, the device 10 can not require a vent 64, 74 if such would interfere with forming a vacuum.

[0063] In another embodiment, illustrated in FIGS. 3 and 4, a pre-chamber 14 of suitable size is formed which opens to the penetration probe 12 on one end 60 and to the analysis chamber 20 on the other end 62. The end 70 of the analysis chamber 20 opposite to that opening to the pre-chamber 14

opens to a compressible bladder 22. The bladder 22 can be formed separately and attached to the end 70 of the analysis chamber 20. Alternatively, it can be formed by removing a section on the middle laminate 82 in the test strip 10, similar to those described in WO97/00441 (incorporated herein by reference in its entirety), as illustrated in FIGS. 3 and 4.

[0064] In use, the bladder 22 in the strip 10 is compressed by suitable means prior to the penetration probe 12 being inserted into the patient. Insertion of the penetration probe 12 can be confirmed by use of a sensor, such as a pressure sensor, or the patient can confirm that the penetration probe 12 is inserted either visually or by touch. In the latter case, the patient sensing can signal the meter, such as by pushing a button. At this point, the means compressing the bladder 22 is withdrawn to a halfway position to draw sample into the pre-chamber 14. When the pre-chamber 14 is full, as indicated by a suitable sensor, the meter indicates to the patient to withdraw the penetration probe 12. The compressing means then moves to its fully withdrawn position and so draws the sample from the pre-chamber 14 into the analysis chamber 20. In the case where the initial suction from the bladder 22 causes the sample to be accumulated with sufficient speed, the pre-chamber 14 can be dispensed with and the bladder 22 used to draw sample through the penetration probe 12 directly into the analysis chamber 20. A vent 64, 74 which would interfere with forming a vacuum need not be incorporated into the device in some embodiments.

[0065] Analysis Chamber

[0066] In a preferred embodiment, the analysis chamber 20 is contained in an analyzing device 10 comprising a disposable analysis strip similar to that disclosed in WO97/00441. The analysis strip of WO97/00441 contains a biosensor for determining the concentration of an analyte in a carrier, e.g., the concentration of glucose in a fluid sample. The electrochemical analysis cell 20 in this strip has an effective volume of 1.5 μ l or less, and can comprise a porous membrane, a working electrode on one side of the membrane, and a counter/reference electrode on the other side. In a preferred embodiment, an analysis cell 20 having an effective volume of about 0.02 μ l or greater is used. More preferably, the cell 20 has a volume ranging from about 0.1 μ l to about 0.5 μ l.

[0067] In one aspect of this embodiment, the penetration probe 12 is a small needle integrated into the analysis strip 10 by being inserted through a wall of the analysis chamber 20 such that one end of the needle 12 opens into the strip analysis chamber 20. In using a device 10 having this arrangement to obtain and analyze a sample of interstitial fluid, the needle 12 is inserted into the patient's dermal layer and sample is drawn into the needle 12 via capillary action. The sample is then transferred from the needle 12 into the analysis chamber 20 by capillary action whereupon the sample is analyzed. An opening 64 in the analysis chamber 20 to atmosphere, remote from the point where the needle 12 opens into the chamber, acts as a vent 64 to allow the escape of displaced air as the analysis chamber 20 fills with sample. Analysis devices of the type disclosed in WO97/00441 are particularly suited for use with this arrangement because of their ability to utilize the very small volumes of sample typically available with interstitial fluid sampling.

[0068] The analysis chamber 20 can contain one or more substances to enhance or diminish the capillary force exerted

by the walls of analysis chamber **20**. Such materials can include polymers, resins, powders, meshes, fibrous materials, crystalline materials, porous materials, or a mixture or combination thereof, as can also be used in the pre-chamber, discussed above. For example, the walls **24** of the analysis chamber **20** can be coated with a hydrophilic material to encourage the flow of fluid sample into the analysis chamber. Suitable hydrophilic materials include polyethylene glycol, polyvinylpyrrolidone, a surfactant, a hydrophilic block copolymer, and polyacrylic acid. The analysis chamber **20** can also contain reagents capable of reacting with the analyte or other substances present in the sample. Such other substances can include substances which interfere in determining the presence or absence of the analyte. In such cases, the reagent will react with the substance so that it no longer interferes with the analysis.

[0069] Any analyte present in a fluid sample in a detectable amount can be analyzed using the device **10**. A typical analytes can include, but is not limited to, an ion, an element, a sugar, an alcohol, a hormone, a protein, an enzyme, a cofactor, a nucleic acid sequence, a lipid, and a drug. In a preferred embodiment, glucose is the analyte to be tested. Typical analytes could include, but are not limited to, ethanol, potassium ion, pharmaceuticals, drugs, cholesterol, and lactate.

[0070] The presence or absence of the analyte can be determined directly. Alternatively, the analyte can be determined by reacting the analyte with one or more reagents present in the analysis chamber. The product of that reaction, indicative of the presence or absence of the analyte, would then be detected. Suitable reaction products include, but are not limited to, a color indicator, an electric current, an electric potential, an acid, a base, a precipitate, or a gas.

[0071] Any suitable analytical method can be used for determining the presence or absence of the analyte or a reaction product of the analyte. Suitable analytical methods include, but are not limited to, electrochemical methods, photoabsorption detection methods, photoemission detection methods, and the measurement of magnetic susceptibility. In the case of a reaction product having a different color than the analyte, or the formation of a precipitate or a gas, a visual determination can be a suitable method for determining the presence or absence of the analyte.

[0072] With reference to FIGS. **7** to **10** there is shown a first embodiment of apparatus of the invention, in this case a biosensor for determining glucose in blood. The embodiment comprises a thin strip membrane **1** having upper and lower surfaces **2, 3** and having a cell zone **4** defined between a working electrode **5** disposed on upper surface **2** and a counter electrode **6** disposed on lower surface **3**. The membrane thickness is selected so that the electrodes are separated by a distance "I" which is sufficiently close that the products of electrochemical reaction at the counter electrode migrate to the working electrode during the time of the test and a steady state diffusion profile is substantially achieved. Typically, "I" will be less than **500** μm . A sample deposition or "target" area **7** defined on upper surface **2** of membrane **1** is spaced at a distance greater than the membrane thickness from cell zone **4**. Membrane **1** has a diffusion zone **8** extending between target area **7** and cell zone **4**. A suitable reagent including a redox mediator "M", an enzyme "E" and a pH buffer "B" are contained within cell zone **4** of the

membrane and/or between cell zone **4** and target area **7**. The reagent may also include stabilisers and the like.

[0073] In some cases it is preferable to locate the enzyme and mediator and/or the buffer in different zones of the membrane. For example the mediator may be initially located within electrochemical cell zone **4** while the enzyme may be situated below target area **7** or in diffusion zone **8**.

[0074] Haemoglobin releases oxygen at low pH's, but at higher pH's it binds oxygen very firmly. Oxygen acts as a redox mediator for glucose oxidase dehydrogenase (GOD). In a glucose sensor this competes with the redox mediator leading to low estimates of glucose concentration. Therefore if desired a first pH buffer can be contained in the vicinity of target area **7** to raise the pH to such a level that all the oxygen is bound to haemoglobin. Such a pH would be non-optimal for GOD/glucose kinetics and would consequently be detrimental to the speed and sensitivity of the test.

[0075] In a preferred embodiment of the invention a second pH buffer is contained as a reagent in the vicinity of the working electrode to restore the pH to kinetically optimal levels.

[0076] The use of a second buffer does not cause oxygen to be released from the haemoglobin as the haemoglobin is contained within the blood cells which are retained near blood target area **7** or are retarded in diffusion in comparison with the plasma and therefore not influenced by the second buffer. In this manner oxygen interference may be greatly reduced or eliminated.

[0077] In use of the sensor a drop of blood containing a concentration of glucose to be determined is placed on target zone **7**. The blood components wick towards cell zone **4**, the plasma component diffusing more rapidly than red blood cells so that a plasma front reaches cell zone **4** in advance of blood cells.

[0078] When the plasma wicks into contact with the reagent, the reagent is dissolved and a reaction occurs that oxidises the analyte and reduces the mediator. After allowing a predetermined time to complete this reaction an electric potential difference is applied between the working electrode and the counter electrode. The potential of the working electrode is kept sufficiently anodic such that the rate of electrooxidation of the reduced form of the mediator at the working electrode is determined by the rate of diffusion of the reduced form of the mediator to the working electrode, and not by the rate of electron transfer across the electrode/solution interface.

[0079] In addition the concentration of the oxidised form of the mediator at the counter electrode is maintained at a level sufficient to ensure that when a current flows in the electrochemical cell the potential of the counter electrode, and thus also the potential of the working electrode, is not shifted so far in the cathodic direction that the potential of the working electrode is no longer in the diffusion controlled region. That is to say, the concentration of the oxidized form at the counter electrode must be sufficient to maintain diffusion controlled electrooxidation of the reduced form of the mediator at the working electrode.

[0080] The behavior of a thin layer cell is such that if both oxidised and reduced forms of the redox couple are present,

eventually a steady state concentration profile is established across the cell. This results in a steady state current. It has been found that by comparing a measure of the steady state current with the rate at which the current varies in the current transient before the steady state is achieved, the diffusion coefficient of the redox mediator can be measured as well as its concentration.

[0081] More specifically, by solving the diffusion equations for this situation it can be shown that over a restricted time range a plot of $\ln(i/i-1)$ vs. time (measured in seconds) is linear and has a slope (denoted by S) which is equal to $-4\pi^2 D/l^2$, where "i" is the current at time "t", "V" is the steady state current, "D" is the diffusion coefficient in cm^2/sec , "l" is the distance between the electrodes in cm and " π " is approximately 3.14159. The concentration of reduced mediator present when the potential was applied between the electrodes is given by $2\pi^2 i / FAIS$, where "T" is Faraday's constant, "A" is the working electrode area and the other symbols are as given above. As this later formula uses S it includes the measured value of the diffusion coefficient.

[0082] Since I is a constant for a given cell, measurement of i as a function of time and i enable the value of the diffusion coefficient of the redox mediator to be calculated and the concentration of the analyte to be determined.

[0083] Moreover the determination of analyte concentration compensates for any variation to the diffusion coefficient of the species which is electrooxidised or electroreduced at the working electrode. Changes in the value of the diffusion coefficient may occur as a result of changes in the temperature and viscosity of the solution or variation of the membrane permeability. Other adjustments to the measured value of the concentration may be necessary to account for other factors such as changes to the cell geometry, changes to the enzyme chemistry or other factors which may effect the measured concentration. If the measurement is made on plasma substantially free of haematocrit (which if present causes variation in the diffusion coefficient of the redox mediator) the accuracy of the method is further improved.

[0084] Each of electrodes 5, 6 has a predefined area. In the embodiments of FIGS. 7 to 10 cell zone 4 is defined by edges 9, 10, 11 of the membrane which correspond with edges of electrodes 5, 6 and by leading (with respect to target area 7) edges 12, 13 of the electrodes. In the present example the electrodes are about 600 angstrom thick and are from 1 to 5 mm wide.

[0085] Optionally, both sides of the membrane are covered with the exception of the target area 7 by laminating layers 14 (omitted from plan views) which serves to prevent evaporation of water from the sample and to provide mechanical robustness to the apparatus. Evaporation of water is undesirable as it concentrates the sample, allows the electrodes to dry out, and allows the solution to cool, affecting the diffusion coefficient and slowing the enzyme kinetics, although diffusion coefficient can be estimated as above.

[0086] A second embodiment according to the invention, shown in FIGS. 11 and 12, differs from the first embodiment by inclusion of a second working electrode 25 and counter/reference electrode 26 defining a second cell zone 24 therebetween. These electrodes are also spaced apart by

less than 500 μm in the present example. Second electrodes 25, 26 are situated intermediate cell zone 4 and target area 7. In this embodiment the redox mediator is contained in the membrane below or adjacent to target area 7 or intermediate target area 7 and first cell zone 4. The enzyme is contained in the membrane in the first cell zone 4 and second cell zone 24. The enzyme does not extend into second cell 24. In this case when blood is added to the target area, it dissolves the redox mediator. This wicks along the membrane so that second electrochemical cell 24 contains redox mediator analyte and serum including electrochemically interfering substances. First electrochemical cell receives mediator, analyte, serum containing electrochemically interfering substances, and enzyme.

[0087] Potential is now applied between both working electrodes and the counter electrode or electrodes but the change in current with time is measured separately for each pair. This allows the determination of the concentration of reduced mediator in the absence of analyte plus the concentration of electrochemically interfering substances in the second electrochemical cell and the concentration of these plus analyte in the first electrochemical cell. Subtraction of the one value from the other gives the absolute concentration of analyte.

[0088] The same benefit is achieved by a different geometry in the embodiment of FIGS. 13 and 14 in which the second working electrode and second counter/reference electrode define the second cell 24 on the side of target area 7 remote from first electrochemical cell 4. In this case the enzyme may be contained in the membrane strip between the target area and cell 1. The redox mediator may be in the vicinity of the target area or between the target area and each cell. The diffusion coefficient of mediator is lowered by undissolved enzyme and the arrangement of FIGS. 13 and 14 has the advantage of keeping enzyme out of the thin layer cells and allowing a faster test (as the steady state current is reached more quickly). Furthermore the diffusion constant of redox mediator is then the same in both thin layer cells allowing more accurate subtraction of interference.

[0089] Although the embodiments of FIGS. 7 to 14 are unitary sensors, it will be understood that a plurality of sensors may be formed on a single membrane as shown in the embodiment of FIGS. 15 to 17. In this case the electrodes of one sensor are conductively connected to those of an adjacent sensor. Sensors may be used successively and severed from the strip after use.

[0090] In the embodiment of FIGS. 15 to 17 electrode dimensions are defined in the diffusion direction (indicated by arrow) by the width of the electrode in that direction.

[0091] The effective dimension of the electrode in a direction transverse to diffusion direction is defined between compressed volumes 16 of the membrane in a manner more fully described in co-pending Application PCT/AU96/00210. For clarity optional laminated layer 14 of FIG. 7 has been omitted from FIGS. 15 to 17.

[0092] In the embodiment of FIG. 18 there is shown a hollow cell according to the invention wherein the electrodes 5, 6 are supported by spaced apart polymer walls 30 to define a hollow cell. An opening 31 is provided on one side of the cell whereby a sample can be admitted into cavity 32. In this embodiment a membrane is not used. As in

previous embodiments, the electrodes are spaced apart by less than 500 μm , preferably 20-400 μm and more preferably 20-200 μm . Desirably the effective cell volume is 1.5 microlitres or less.

[0093] It will be understood that the method of the invention may be performed with a cell constructed in accord with co-pending application PCT/AU95/00207 or cells of other known design, provided these are modified to provide a sufficiently small distance between electrode faces.

[0094] The method of the invention will now be further exemplified with reference to **FIGS. 19 and 20**.

[0095] A membrane 130 microns thick was coated on both sides with a layer of Platinum 60 nanometers thick. An area of 12.6 sq. mm was defined by compressing the membrane. 1.5 microlitres of a solution containing 0.2 Molar potassium ferricyanide and 1% by weight glucose oxidase dehydrogenase was added to the defined area of the membrane and the water allowed to evaporate.

[0096] The platinum layers were then connected to a potentiostat to be used as the working and counter/reference electrodes. 3 microlitres of an aqueous solution containing 5 millimolar D-glucose and 0.9 wt % NaCl was dropped on to the defined area of the membrane. After an elapse of 20 seconds a voltage of 300 millivolts was applied between the working and counter/reference electrodes and the current recorded for a further 30 seconds at intervals of 0.1 seconds.

[0097] **FIG. 19** is a graph of current versus time based on the above measurements.

[0098] Using a value of the steady state current of 26.9 microamps the function $\ln(i/26.9-1)$ was computed and plotted versus time. The slope of the graph (**FIG. 20**) is -0.342, which corresponds to a diffusion coefficient of $1.5 \times 10^{-6} \text{ cm}^2$ per second and a corrected glucose concentration (subtracting background ferrocyanide) of 5.0 millimolar.

[0099] The steady state current is one in which no further significant current change occurs during the test. As will be understood by those skilled in the art, a minimum current may be reached after which there may be a drift due to factors such as lateral diffusion, evaporation, interfering electrochemical reactions or the like. However, in practice it is not difficult to estimate the "steady state" current (i). One method for doing so involves approximating an initial value for i. Using the fit of the i versus t data to the theoretical curve a better estimate of i is then obtained. This is repeated reiteratively until the measured value and approximated value converge to within an acceptable difference, thus yielding an estimated i.

[0100] In practice, the measurements of current i at time t are made between a minimum time t_{min} and a maximum time t_{max} after the potential is applied. The minimum and maximum time are determined by the applicability of the equations and can readily be determined by experiment of a routine nature. If desired the test may be repeated by switching off the voltage and allowing the concentration profiles of the redox species to return towards their initial states.

[0101] It is to be understood that the analysis of the current v. time curve to obtain values of the Diffusion Coefficient

and/or concentration is not limited to the method given above but could also be achieved by other methods.

[0102] For instance, the early part of the current v. time curve could be analysed by the Cottrell equation to obtain a value of $D^{1/2} \times Co$ (Co =Concentration of analyte) and the steady state current analysed to obtain a value of $D \times Co$. These two values can then be compared to obtain D and C separately.

[0103] It will be understood that in practice of the invention an electrical signal is issued by the apparatus which is indicative of change in current with time. The signal may be an analogue or digital signal or may be a series of signals issued at predetermined time intervals. These signals may be processed by means of a microprocessor or other conventional circuit to perform the required calculations in accordance with stored algorithms to yield an output signal indicative of the diffusion coefficient, analyte concentration, haematocrit concentration or the like respectively. One or more such output signals may be displayed by means of an analogue or digital display.

[0104] It is also possible by suitable cell design to operate the cell as a depletion cell measuring the current required to deplete the mediator. For example in the embodiment of **FIG. 5** the method of the invention may be performed using electrodes **5, 6**, which are spaced apart by less than 500 μm . An amperometric or voltammetric depletion measurement may be made using electrodes **5** and **26** which are spaced apart more than 500 μm and such that there is no interference between the redox species being amperometrically determined at electrodes **5, 26**.

[0105] The depletion measurement may be made prior to, during or subsequent to, the measurement of diffusion coefficient by the method of the invention. This enables a substantial improvement in accuracy and reproducibility to be obtained.

[0106] In the embodiments described the membrane is preferably an asymmetric porous membrane of the kind described in Patent No. 4,629,563 and 4,774,039. However symmetrical porous membranes may be employed. The membrane may be in the form of a sheet, tube, hollow fibre or other suitable form.

[0107] If the membrane is asymmetric the target area is preferably on the more open side of the asymmetric membrane. The uncompressed membrane desirably has a thickness of from 20 to 500 μm . The minimum thickness is selected having regard to speed, sensitivity, accuracy and cost. If desired a gel may be employed to separate haematocrit from GOD. The gel may be present between the electrodes and/or in the space between the sample application area and the electrodes.

[0108] The working electrode is of any suitable metal for example gold, silver, platinum, palladium, iridium, lead, a suitable alloy. The working electrode may be preformed or formed in situ by any suitable method for example sputtering, evaporation under partial vacuum, by electrodeless plating, electroplating, or the like. Suitable non-metal conductors may also be used for electrode construction. For example, conducting polymers such as poly(pyrrole), poly(aniline), porphyrin "wires", poly(isoprene) and poly(cis-butadiene) doped with iodine and "ladder polymers".

Other non-metal electrodes may be graphite or carbon mixed with a binder, or a carbon filled plastic.

[0109] Inorganic electrodes such as In_2O_3 or SnO_2 may also be used. The counter/reference electrode may for example be of similar construction to the working electrode. Nickel hydroxide or a silver halide may also be used to form the counter/reference electrode.

[0110] Silver chloride may be employed but it will be understood that chloridisation may not be necessary and silver may be used if sufficient chloride ions are present in the blood sample. Although in the embodiments described the working electrode is shown on the upper surface of the biosensor and the counter/reference electrode is on the lower surface, these may be reversed.

[0111] It is preferable that the working electrode and counter (or counter/reference) electrodes are of substantially the same effective geometric area.

[0112] If a separate reference and counter electrode are employed, they may be of similar construction. The reference electrode can be in any suitable location.

[0113] It will be understood that the features of one embodiment herein described may be combined with those of another. The invention is not limited to use with any particular combination of enzyme and mediator and combinations such as are described in EP0351892 or elsewhere may be employed. The system may be used to determine analytes other than glucose (for example, cholesterol) by suitable adaptation of reagents and by appropriate membrane selection. The system may also be adapted for use with media other than blood. For example the method may be employed to determine the concentration of contaminants such as chlorine, iron, lead, cadmium, copper, etc., in water.

[0114] Although the cells herein described have generally planar and parallel electrodes it will be understood that other configurations may be employed, for example one electrode could be a rod or needle and the other a concentric sleeve.

[0115] Display/Storage of Measurement Data

[0116] In a preferred embodiment, an analysis strip as described above or another embodiment of the sampling device **10** is integrated with a measuring device, e.g., a meter, which can display, store or record test data, optionally in computer-readable format. In such an embodiment, the test strip **10** comprises an interface for communicating with the meter, e.g., conductive leads from the electrodes of the electrochemical cell **20**. In the case of obtaining an electrochemical measurement, the interface communicates a voltage or a current to the electrochemical cell **20**.

[0117] The above description discloses several methods and materials of the present invention. This invention is susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention as embodied in the attached claims.

What is claimed is:

1. A fluid sampling device, the device comprising a body, the body comprising:

a dermal layer penetration probe having a penetrating end and a communicating end, the penetration probe having a volume; and

an analysis chamber having a proximal end and a distal end, the analysis chamber having a volume, wherein the volume of the penetration probe is greater than the volume of the analysis chamber, and wherein the penetration probe is in fluid communication with the analysis chamber such that fluid can flow from the penetration probe to the analysis chamber.

2. The device of claim 1, wherein the penetration probe is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force, and wherein a differential in capillary force exists between the first capillary force and the second capillary force.

3. The device of claim 2, wherein the second capillary force is greater than the first capillary force.

4. The device of claim 3, wherein an interior surface of the penetration probe comprises a first penetration probe wall and a second penetration probe wall, wherein the first penetration probe wall and the second penetration probe wall are spaced apart at a first distance to define a penetration probe height, and wherein an interior surface of the analysis chamber comprises a first analysis chamber wall and a second analysis chamber wall, wherein the first analysis chamber wall and the second analysis chamber wall are spaced apart at a second distance to define an analysis chamber height, wherein the analysis chamber height is less than the penetration probe height, and wherein the differential in capillary force derives at least in part from a difference between the penetration probe height and the analysis chamber height.

5. The device of claim 3, wherein at least one of the penetration probe and the analysis chamber comprises a substance capable of enhancing or diminishing a capillary force.

6. The device of claim 5, wherein the substance is selected from the group consisting of a polymer, a resin, a powder, a mesh, a fibrous material, a crystalline material, a porous material, and a combination thereof.

7. The device of claim 6, wherein the substance is selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, a surfactant, a hydrophilic block copolymer, and polyvinylacetate.

8. The device of claim 1, wherein the penetration probe comprises a first penetration probe wall and a second penetration probe wall and wherein the analysis chamber comprises a first analysis chamber wall and a second analysis chamber wall, and wherein the distance between the first penetration probe wall and the second penetration probe wall is greater than the distance between the first analysis chamber wall and the second analysis chamber wall.

9. The device of claim 1, wherein the penetration probe comprises a component selected from the group consisting of a needle, a lancet, a tube, a channel, and a solid protrusion.

10. The device of claim 1, wherein the device has a proximal edge, the proximal edge comprising a recess, wherein the penetration probe is positioned within the recess.

11. The device of claim 10, wherein the recess is configured to substantially align with a shape of a selected dermal surface.

12. The device of claim 1, further comprising a releasable actuator, wherein the actuator is capable of supplying a force sufficient to cause the penetration probe to penetrate a dermal layer.

13. The device of claim 12, wherein the actuator is external to the body, and wherein upon release the actuator propels the body to the dermal layer.

14. The device of claim 12, wherein the actuator is integral with the body.

15. The device of claim 14, wherein upon release the actuator propels the penetration probe toward the dermal layer.

16. The device of claim 1, wherein the analysis chamber comprises an electrochemical cell, the cell comprising a working electrode and a counter/reference electrode.

17. The device of claim 1, further comprising an interface for communication with a meter.

18. The device of claim 17, wherein the interface communicates a voltage or a current.

19. The device of claim 1, wherein the analysis chamber comprises a hollow electrochemical cell, the hollow electrochemical cell comprising a working electrode, a counter or reference electrode, and an opening for admitting an analyte to the cell, the working electrode being spaced from the counter or reference electrode by a distance of less than 500 μm .

20. The device of claim 19, wherein the penetration probe comprises a component selected from the group consisting of a needle, a lancet, a tube, a channel, and a solid protrusion.

21. The device of claim 19, wherein the penetration probe is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force and wherein a differential exists between the first capillary force and the second capillary force.

22. The device of claim 21, wherein the second capillary force is greater than the first capillary force.

23. The device of claim 1, wherein a distal end of the penetration probe is interfaced with the proximal end of the analysis chamber.

24. The device of claim 1, wherein a distal end of the penetration probe is integrated with the proximal end of the analysis chamber.

25. A fluid sampling device comprising a body, the body comprising

a dermal layer penetration probe having a penetrating end and a communicating end;

an analysis chamber having a proximal end and a distal end, the analysis chamber having a volume, wherein the analysis chamber comprises a hollow electrochemical cell, the hollow electrochemical cell comprising a working electrode, a counter or reference electrode, and an opening for admitting an analyte to the cell, the working electrode being spaced from the counter or reference electrode by a distance of less than 500 μm ; and

a pre-chamber having a proximal end and a distal end, the pre-chamber having a volume, wherein the pre-chamber is interposed between the penetration probe and the analysis chamber such that the proximal end of the

pre-chamber is adjacent the communicating end of the penetration probe and the distal end of the pre-chamber is adjacent the proximal end of the analysis chamber, wherein the volume of the pre-chamber is greater than the volume of the analysis chamber, and wherein the penetration probe is in fluid communication with the analysis chamber such that fluid can flow from the penetration probe to the analysis chamber.

26. The device of claim 25, wherein the penetration probe comprises a component selected from the group consisting of a needle, a lancet, a tube, a channel, and a solid protrusion.

27. The device of claim 25, wherein the pre-chamber is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force and wherein a differential in capillary force exists between the first capillary force and the second capillary force.

28. The device of claim 27, wherein the second capillary force is greater than the first capillary force.

29. The device of claim 25, wherein the distal end of the pre-chamber is interfaced with the proximal end of the analysis chamber.

30. The device of claim 25, wherein the distal end of the pre-chamber is integrated with the proximal end of the analysis chamber.

31. A method for measuring a quantity of an analyte in a fluid sample, the method comprising the steps of:

providing a fluid sampling device, the sampling device comprising:

a dermal layer penetration probe, having a penetrating end and a communicating end;

an analysis chamber having a proximal end and a distal end, the analysis chamber having a volume, wherein the penetration probe is in fluid communication with the analysis chamber such that a fluid sample can flow from the penetration probe to the analysis chamber; and

a pre-chamber having a proximal end and a distal end, the pre-chamber having a volume, wherein the pre-chamber is interposed between the penetration probe and the analysis chamber such that the proximal end of the pre-chamber is adjacent the communicating end of the penetration probe and the distal end of the pre-chamber is adjacent the proximal end of the analysis chamber, and wherein the volume of the pre-chamber is greater than the volume of the analysis chamber;

penetrating a dermal layer with the penetration probe;

substantially filling the analysis chamber with the fluid sample by allowing the sample to flow from the penetration probe to the analysis chamber; and

measuring a quantity of an analyte in the fluid sample.

32. The method of claim 31, wherein the sample is selected from the group consisting of interstitial fluid and whole blood.

33. The method of claim 31, wherein the analyte is selected from the group consisting of an ion, an element, a sugar, an alcohol, a hormone, a protein, an enzyme, a cofactor, a nucleic acid sequence, a lipid, a pharmaceutical, and a drug.

34. The method of claim 31, wherein the analyte is selected from the group consisting of potassium ion, ethanol, cholesterol, glucose, and lactate.

35. The method of claim 31, wherein a flow of fluid sample to the analysis chamber is driven by a driving force, wherein the driving force comprises a force selected from the group consisting of a capillary force and a pressure differential.

36. The method of claim 31, wherein the pre-chamber is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force and wherein a differential in capillary force exists between the first capillary force and the second capillary force.

37. The method of claim 31, wherein the second capillary force is greater than the first capillary force.

38. The method of claim 31, wherein an interior surface of the pre-chamber comprises a first pre-chamber wall and a second pre-chamber wall, wherein the first pre-chamber wall and the second pre-chamber wall are spaced apart at a first distance to define a pre-chamber height, and wherein an interior surface of the analysis chamber comprises a first analysis chamber wall and a second analysis chamber wall spaced apart at a second distance to define an analysis chamber height, wherein the analysis chamber height is less than the pre-chamber height, wherein the pre-chamber is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force, and wherein a differential in the first capillary force and the second capillary force derives at least in part from a difference between the pre-chamber height and the analysis chamber height.

39. The method of claim 31, wherein at least one of the pre-chamber and the analysis chamber comprises a substance capable of enhancing or diminishing a capillary force.

40. The method of claim 39, wherein the substance is selected from the group consisting of a polymer, a resin, a powder, a mesh, a fibrous material, a crystalline material, a porous material, and a combination thereof.

41. The method of claim 39, wherein the substance is selected from the group consisting of polyethylene glycol, polyvinyl pyrrolidone, a surfactant, a hydrophilic block copolymer, and polyacrylic acid.

42. The method of claim 35, wherein the pressure differential comprises a positive pressure applied to the analysis chamber.

43. The method of claim 35, wherein the pressure differential comprises a negative pressure applied from the analysis chamber.

44. The method of claim 31, wherein the analysis chamber comprises a hollow electrochemical cell, the hollow electrochemical cell comprising a working electrode, a counter or reference electrode, and an opening for admitting an analyte to the cell, the working electrode being spaced from the counter or reference electrode by a distance of less than 500 μm .

45. The method of claim 44, wherein the penetration probe comprises a component selected from the group consisting of a needle, a lancet, a tube, a channel, and a solid protrusion.

46. The method of claim 44, wherein the pre-chamber is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force and wherein a differential in capillary force exists between the first capillary force and the second capillary force.

47. The method of claim 44, wherein the second capillary force is greater than the first capillary force.

48. A method for measuring a quantity of an analyte in a fluid sample, the method comprising the steps of:

providing a fluid sampling device, the device comprising:

a dermal layer penetration probe having a penetrating end and a communicating end, the penetration probe having a volume;

an analysis chamber having a proximal and distal end, the analysis chamber having a volume, wherein the volume of the penetration probe is greater than the volume of the analysis chamber, wherein the penetration probe is in fluid communication with the analysis chamber such that a fluid sample can flow from the penetration probe to the analysis chamber; penetrating a dermal layer with the penetration probe; substantially filling the analysis chamber with a fluid sample by allowing the

sample to flow from the penetration probe to the analysis chamber; and measuring a quantity of an analyte in the fluid sample.

49. The method of claim 48, wherein the sample is selected from the group consisting of interstitial fluid and whole blood.

50. The method of claim 48, wherein the analyte is selected from the group consisting of an ion, an element, a sugar, an alcohol, a hormone, a protein, an enzyme, a cofactor, a nucleic acid sequence, a lipid, a pharmaceutical, and a drug.

51. The method of claim 48, wherein the analyte is selected from the group consisting of potassium ion, ethanol, cholesterol, glucose, and lactate.

52. The method of claim 48, wherein a flow of sample to the analysis chamber is driven by a driving force, wherein the driving force comprises a force selected from the group consisting of a capillary force and a pressure differential.

53. The method of claim 48, wherein the penetration probe is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force and wherein a differential in capillary force exists between the first capillary force and the second capillary force.

54. The method of claim 48, wherein the second capillary force is greater than the first capillary force.

55. The method of claim 48, wherein an interior surface of the penetration probe comprises a first penetration probe wall and a second penetration probe wall, wherein the first penetration probe wall and the second penetration probe wall are spaced apart at a first distance to define a penetration probe height, and wherein an interior surface of the analysis chamber comprises a first analysis chamber wall and a second analysis chamber wall, wherein the first analysis chamber wall and the second analysis chamber wall are spaced apart at a second distance to define an analysis chamber height, wherein the height of the analysis chamber is less than the height of the penetration probe, wherein the penetration probe is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force and wherein a differential in capillary force exists between the first capillary force and the second capillary force, and wherein the differential capillary force

derives at least in part from a difference between the penetration probe height and the analysis chamber height.

56. The method of claim 48, wherein at least one of the penetration probe and the analysis chamber comprises a substance capable of enhancing or diminishing a capillary force.

57. The method of claim 56, wherein the substance is selected from the group consisting of a polymer, a resin, a powder, a mesh, a fibrous material, a crystalline material, a porous material, and a combination thereof.

58. The method of claim 56, wherein the substance is selected from the group consisting of polyethylene glycol, polyvinyl pyrrolidone, a surfactant, a hydrophilic block copolymer, and polyacrylic acid.

59. The method of claim 52, wherein the pressure differential comprises a positive pressure applied to the analysis chamber.

60. The method of claim 52, wherein the pressure differential comprises a negative pressure applied from the analysis chamber.

61. The method of claim 48, wherein the analysis chamber comprises a hollow electrochemical cell, the hollow electrochemical cell comprising a working electrode, a counter or reference electrode, and an opening for admitting an analyte to the cell, the working electrode being spaced from the counter or reference electrode by a distance of less than 500 μm .

62. The method of claim 61, wherein the penetration probe comprises a component selected from the group consisting of a needle, a lancet, a tube, a channel, and a solid protrusion.

63. The method of claim 61, wherein the penetration probe is capable of exerting a first capillary force and the analysis chamber is capable of exerting a second capillary force and wherein a differential in capillary force exists between the first capillary force and the second capillary force.

64. The method of claim 61, wherein the second capillary force is greater than the first capillary force.

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摘要(译)

本申请中公开的发明是一种用于将皮下液体样品（例如组织间液或全血）的取样和分析组合在适于医院床边和家庭使用的装置中的方法和装置。它适用于在流体中以有用的代表性浓度存在的任何分析物，并且特别适用于监测葡萄糖。

