

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 October 2006 (05.10.2006)

PCT

(10) International Publication Number
WO 2006/105146 A2

(51) International Patent Classification:
G01F 1/64 (2006.01) **G01N 33/487** (2006.01)

(21) International Application Number:
PCT/US2006/011382

(22) International Filing Date: 28 March 2006 (28.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/666,775 29 March 2005 (29.03.2005) US
60/743,080 27 December 2005 (27.12.2005) US

(71) Applicant (for all designated States except US): **ARKAL MEDICAL, INC.** [US/US]; 46575 Fremont Boulevard, Fremont, California 94538 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **JINA, Arvind, N.** [US/US]; 3353 Colonna Avenue, San Jose, California 95148 (US).

(74) Agents: **O'REGAN, Cecily, Anne** et al.; **WILSON SON-SINI GOODRICH & ROSATI**, 650 Page Mill Road, Palo Alto, California 94304-1050 (US).

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

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

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

(54) Title: DEVICES, SYSTEMS, METHODS AND TOOLS FOR CONTINUOUS GLUCOSE MONITORING

(57) Abstract: One aspect of the invention provides a glucose monitor having a plurality of tissue piercing elements, each tissue piercing element having a distal opening, a proximal opening and interior space extending between the distal and proximal openings; a sensing area in fluid communication with the proximal openings of the tissue piercing elements; sensing fluid extending from the sensing area into substantially the entire interior space of the tissue piercing elements; and a glucose sensor adapted to detect a concentration of glucose in the sensing fluid within the sensing area. Another aspect of the invention provides a method of in vivo monitoring of an individual's interstitial fluid glucose concentration including the following steps: inserting distal ends of a plurality of tissue piercing elements through a stratum corneum area of the individual's skin, the tissue piercing elements each having a distal opening, a proximal opening, an interior space extending between the distal and proximal openings, and a sensing fluid filling substantially the entire interior space; and sensing a glucose concentration of the sensing fluid.



WO 2006/105146 A2

DEVICES, SYSTEMS, METHODS AND TOOLS FOR CONTINUOUS GLUCOSE MONITORING**CROSS-REFERENCE**

[0001] This application claims the benefit of U.S. Provisional Application No. 60/666,775, filed March 29, 2005, and U.S. Provisional Application No. 60/743,080, filed December 27, 2005, which are incorporated herein by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] The invention relates to systems, devices, and tools, and the use of such systems, devices and tools for monitoring blood glucose levels in a person having diabetes. More specifically, the invention relates to systems, devices, and tools and the use of such systems, devices and tools for monitoring blood glucose level continuously, or substantially continuously.

[0003] Diabetes is a chronic, life-threatening disease for which there is no known cure. It is a syndrome characterized by hyperglycemia and relative insulin deficiency. Diabetes affects more than 120 million people world wide, and is projected to affect more than 220 million people by the year 2020. It is estimated that 1 in 3 children today will develop diabetes sometime during their lifetime. Diabetes is usually irreversible, and can lead to a variety of severe health complications, including coronary artery disease, peripheral vascular disease, blindness and stroke. The Center for Disease Control (CDC) has reported that there is a strong association between being overweight, obesity, diabetes, high blood pressure, high cholesterol, asthma and arthritis. Individuals with a body mass index of 40 or higher are more than 7 times more likely to be diagnosed with diabetes.

[0004] There are two main types of diabetes, Type I diabetes (insulin-dependent diabetes mellitus) and Type II diabetes (non-insulin-dependent diabetes mellitus). Varying degrees of insulin secretory failure may be present in both forms of diabetes. In some instances, diabetes is also characterized by insulin resistance. Insulin is the key hormone used in the storage and release of energy from food.

[0005] As food is digested, carbohydrates are converted to glucose and glucose is absorbed into the blood stream primarily in the intestines. Excess glucose in the blood, e.g. following a meal, stimulates insulin secretion, which promotes entry of glucose into the cells, which controls the rate of metabolism of most carbohydrates.

[0006] Insulin secretion functions to control the level of blood glucose both during fasting and after a meal, to keep the glucose levels at an optimum level. In a normal person blood glucose levels are between 80 and 90 mg/dL of blood during fasting and between 120 to 140 mg/dL during the first hour or so following a meal. For a person with diabetes, the insulin response does not function properly (either due to inadequate levels of insulin production or insulin resistance), resulting in blood glucose levels below 80 mg/dL during fasting and well above 140 mg/dL after a meal.

[0007] Currently, persons suffering from diabetes have limited options for treatment, including taking insulin orally or by injection. In some instances, controlling weight and diet can impact the amount of insulin required, particularly for non-insulin dependent diabetics. Monitoring blood glucose levels is an important process that is used to help diabetics maintain blood glucose levels as near as normal as possible throughout the day.

[0008] The blood glucose self-monitoring market is the largest self-test market for medical diagnostic products in the world, with a size of approximately \$3 billion in the United States and \$5.0 billion worldwide. It is estimated that the worldwide blood glucose self-monitoring market will amount to \$8.0 billion by 2006. Failure to manage the disease properly has dire consequences for diabetics. The direct and indirect costs of diabetes exceed \$130 billion annually in the United States – about 20% of all healthcare costs.

[0009] There are two main types of blood glucose monitoring systems used by patients: single point or non-continuous and continuous. Non-continuous systems consist of meters and tests strips and require blood samples to be drawn from fingertips or alternate sites, such as forearms and legs (e.g. OneTouch® Ultra by LifeScan, Inc., Milpitas, CA, a Johnson & Johnson company). These systems rely on lancing and manipulation of the fingers or alternate blood draw sites, which can be extremely painful and inconvenient, particularly for children.

[0010] Continuous monitoring sensors are generally implanted subcutaneously and measure glucose levels in the interstitial fluid at various periods throughout the day, providing data that shows trends in glucose measurements over a short period of time. These sensors are painful during insertion and usually require the assistance of a health care professional. Further, these sensors are intended for use during only a short duration (e.g., monitoring for a matter of days to determine a blood sugar pattern). Subcutaneously implanted sensors also frequently lead to infection and immune response complications. Another major drawback of currently available continuous monitoring devices is that they require frequent, often daily, calibration using blood glucose results that must be obtained from painful finger-sticks using traditional meters and test strips. This calibration, and re-calibration, is required to maintain sensor accuracy and sensitivity, but it can be cumbersome as well as painful.

[0011] At this time, there are four products approved by the FDA for continuous glucose monitoring, none of which are presently approved as substitutes for current glucose self-monitoring devices. Medtronic (www.medtronic) has two continuous glucose monitoring products approved for sale: Guardian® RT Real-Time Glucose Monitoring System and CGMS® System. Each product includes an implantable sensor that measures and stores glucose values for a period of up to three days. One product is a physician product. The sensor is required to be implanted by a physician, and the results of the data aggregated by the system can only be accessed by the physician, who must extract the sensor and download the results to a personal computer for viewing using customized software. The other product is a consumer product, which permits the user to download results to a personal computer using customized software.

[0012] A third product approved for continuous glucose monitoring is the Gluowatch® developed by Cygnus Inc., which is worn on the wrist like a watch and can take glucose readings every ten to twenty minutes for up to twelve hours at a time. It requires a warm up time of 2 to 3 hours and replacement of the sensor pads every 12 hours. Temperature and perspiration are also known to affect its accuracy. The fourth approved product is a subcutaneously implantable glucose sensor developed by Dexcom, San Diego, CA (www.dexcom.com). All of the approved devices are known to require daily, often frequent, calibrations with blood glucose values which the patient must obtain using conventional finger stick blood glucose monitors.

SUMMARY OF THE INVENTION

[0013] The invention is a novel continuous glucose monitor that may be periodically calibrated without using finger sticks or other invasive calibration techniques and measures glucose without extracting any interstitial fluid (or any other fluid) from the user. The continuous glucose monitor may be configured to be self-calibrating.

[0014] One aspect of the invention provides a glucose monitor with a plurality of tissue piercing elements, each tissue piercing element having a distal opening, a proximal opening and interior space extending between the distal and proximal openings; a sensing area in fluid communication with the proximal openings of the tissue piercing elements; sensing fluid extending from the sensing area into substantially the entire interior space of the tissue piercing elements; and a glucose sensor adapted to detect a concentration of glucose in the sensing fluid within the sensing area. This arrangement permits interstitial fluid glucose to diffuse from the interstitial fluid into the sensing area without extracting interstitial fluid through the distal openings of the piercing elements into the interior space.

In some embodiments, the glucose monitor has a removable cover extending over the distal openings of the tissue piercing elements.

[0015] In some embodiments, the glucose monitor has a display adapted to display a glucose concentration sensed by the sensor. The display may be disposed within a housing separate from the sensor, with the glucose monitor further including a communicator adapted to wirelessly communicate sensor information from the sensor to the display.

[0016] In some embodiments, the glucose monitor includes a sensing fluid reservoir and a pump adapted to move sensing fluid out of the sensing fluid reservoir into the sensing area. Such embodiments may have a manual actuator and may have a waste reservoir adapted to receive sensing fluid from the sensing area. In some such embodiments, the glucose monitor may have a housing with a first part and a second part, the first part of the housing being adapted to support the tissue piercing elements, the sensing fluid reservoir, the sensing area, and at least part of the sensor, the second part of the housing having an electrical connection to the at least part of the sensor in the first part of the housing, with the housing further including a connector adapted to connect and disconnect the first part of the housing from the second part of the housing. In some embodiments, the first part of the housing is further adapted to support the pump and optionally the waste reservoir. Some embodiments have a communicator supported by the second part of the housing and adapted to communicate sensor information to a display.

[0017] In some embodiments, the sensing fluid in the sensing fluid reservoir has a glucose concentration of between about 0 mg/dl and about 400 mg/dl. The sensing fluid may also contain buffers, preservatives or other materials in addition to the glucose. In yet other embodiments, the glucose monitor has an adhesive element adjacent the tissue piercing elements and adapted to attach to a user's skin. The glucose sensor, tissue piercing elements and sensing area may be further adapted to detect a concentration of glucose in the sensing fluid within the sensing area without extracting interstitial fluid through the distal openings into the interior space.

[0018] Another aspect of the invention provides a method of in vivo monitoring of an individual's interstitial fluid glucose concentration including the following steps: inserting distal ends of a plurality of tissue piercing elements through a stratum corneum area of the individual's skin, the tissue piercing elements each having a distal opening, a proximal opening, an interior space extending between the distal and proximal openings, and a sensing fluid filling substantially the entire interior space; and sensing a glucose concentration of the sensing fluid. This method permits interstitial fluid glucose to diffuse from the interstitial fluid into the sensing area without extracting interstitial fluid through the distal openings of the piercing elements into the interior space. Some embodiments include the step of removing a cover from the distal openings of the tissue piercing elements prior to the inserting step. Some embodiments include the step of displaying glucose concentration information remote from the stratum corneum area of the individual's skin. The method may also include the step of wirelessly communicating glucose concentration information to a display.

[0019] In some embodiments, the sensing step is performed by a sensor in fluid communication with a sensing area and the interior spaces of the tissue piercing elements, and the method further includes the step of calibrating the sensor by moving sensing fluid into the sensing area, such as by using a pump. The method may also include the step of moving sensing fluid out of the sensing area as sensing fluid is moved into the sensing area. The sensing fluid may have a glucose concentration of between about 0 mg/dl and about 400 mg/dl.

[0020] In embodiments in which the step of moving sensing fluid includes the steps of moving sensing fluid from a sensing fluid reservoir, the sensing fluid reservoir, sensing area, tissue piercing elements and at least part of the sensor may be supported by a first part of a housing, and the method further includes the step of attaching the first part of the housing to a second part of the housing prior to the inserting step, with the second part of the housing

having an electrical connection to the at least part of the sensor in the first part of the housing. The method may also include the step of separating the second part of the housing from the first part of the housing after the sensing step.

[0021] In some embodiments, the method includes the step of attaching the tissue piercing elements to the individual with adhesive. In other embodiments, the method includes the step of permitting glucose to diffuse from interstitial fluid of the individual through the distal openings into the interior space.

[0022] Another embodiment of the invention includes a glucose monitor comprising a plurality of tissue piercing elements, each tissue piercing element comprising a distal opening, a proximal opening and an interior space extending between the distal and proximal openings; a sensing area in continuous fluid communication with the proximal openings of the tissue piercing elements; sensing fluid extending from the sensing area into substantially the entire interior space of the tissue piercing elements; and a glucose sensor adapted to continuously detect a concentration of glucose in the sensing fluid within the sensing area further adapted to be self-calibrating.

[0023] Other embodiments of the invention will be apparent from the specification and drawings.

INCORPORATION BY REFERENCE

[0024] All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0026] **Figure 1** is a cross-sectional schematic view of a glucose monitoring device according to one embodiment of the invention in place on a user's skin.

[0027] **Figure 2** shows an exploded view of a glucose monitoring device according to another embodiment of the invention.

[0028] **Figures 3(a) and (b)** are a schematic representative drawing of a three electrode system for use with the glucose sensor of one embodiment of this invention.

[0029] **Figures 4(a) and (b)** are a schematic representative drawing of a two electrode system for use with the glucose sensor of one embodiment of this invention.

[0030] **Figure 5** is a cross-sectional schematic view of a portion of a glucose monitoring device according to yet another embodiment of the invention.

[0031] **Figure 6** shows a remote receiver for use with a glucose monitoring system according to yet another embodiment of the invention.

[0032] **Figure 7** shows a glucose sensor in place on a user's skin and a remote monitor for use with the sensor.

DETAILED DESCRIPTION OF THE INVENTION

[0033] The present invention provides a significant advance in biosensor and glucose monitoring technology: portable, virtually non-invasive, self-calibrating, integrated and non-implanted sensors which continuously indicate the user's blood glucose concentration, enabling swift corrective action to be taken by the patient. The sensor and monitor of this invention may be used to measure other analytes as well, such as electrolytes like sodium or

potassium ions. As will be appreciated by persons of skill in the art, the glucose sensor can be any suitable sensor including, for example, an electrochemical sensor an optical sensor.

[0034] Figure 1 shows a schematic cross-section of one embodiment of the invention in use. The glucose monitor 100 has an array of unique hollow microneedles 102 or other tissue piercing elements extending through the stratum corneum 104 of a user into the interstitial fluid 106 beneath the stratum corneum. Suitable microneedle arrays include those described in Stoeber et al. US Patent 6,406,638; US Patent Appl. Publ. No. 2005/0171480; and US Patent Appl. Publ. No. 2006/0025717. The needles in array 102 are hollow and have open distal ends, and their interiors communicate with a sensing area 110 within a sensor channel 108. Sensing area 110 is therefore in fluid communication with interstitial fluid 106 through microneedle array 102. In this embodiment, sensing area 110 and the microneedles 102 are pre-filled with sensing fluid prior to the first use of the device. Thus, when the device is applied to the user's skin and the microneedles pierce the stratum corneum of the skin, there is substantially no net fluid transfer from the interstitial fluid into the microneedles. Rather, glucose diffuses from the interstitial fluid into the sensing fluid within the needles, as described below.

[0035] Disposed above and in fluid communication with sensor channel 108 is a glucose sensor 112. In some embodiments, glucose sensor is an electrochemical glucose sensor that generates an electrical signal (current, voltage or charge) whose value depends on the concentration of glucose in the fluid within sensing area 110. Details of the operation of glucose sensor 112 are discussed in more detail below.

[0036] Sensor electronics element 114 receives the voltage signal from sensor 112. In some embodiments, sensor electronics element 114 uses the sensed signal to compute a glucose concentration and display it. In other embodiments, sensor electronics element 114 transmits the sensed signal, or information derived from the sensed signal, to a remote device, such as through wireless communication. Glucose monitor 100 is held in place on the skin 104 by one or more adhesive pads 116.

[0037] Glucose monitor 100 has a novel built-in sensor calibration system. A reservoir 118 containing a sensing fluid having, e.g., a glucose concentration between about 0 and about 400 mg/dl. In some embodiments, the glucose concentration in the sensing fluid is selected to be below the glucose sensing range of the sensor. The sensing fluid may also contain buffers, preservatives or other components in addition to the glucose. Upon actuation of a pump manually or automatically, plunger or other actuator 120, sensing fluid is forced from reservoir 118 through a check valve 122 (such as a flap valve) into sensing channel 108. Any sensing fluid within channel 108 is forced through a second check valve 124 (e.g., a flap valve) into a waste reservoir 126. Check valves or similar gating systems are used to prevent contamination. Because the fresh sensing fluid has a known glucose concentration, sensor 112 can be calibrated at this value to set a base line. After calibration, the sensing fluid in channel 108 remains stationary, and glucose from the interstitial fluid 106 diffuses through microneedles 102 into the sensing area 110. Changes in the glucose concentration from over time reflect differences between the calibration glucose concentration of the sensing fluid in the reservoir 118 and the glucose concentration of the interstitial fluid which can be correlated with the actual blood glucose concentration of the user using proprietary algorithms. Because of possible degradation of the sensor or loss of sensor sensitivity over time, the device may be periodically recalibrated by operating actuator 120 manually or automatically to send fresh sensing fluid from reservoir 118 into sensing area 110.

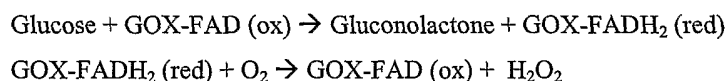
[0038] In some embodiments, microneedle array 102, reservoirs 118 and 126, channel 108, sensor 112 and adhesive pads 116 are contained within a support structure (such as a housing 128) separate from electronics element 114 and actuator 120, which are supported within their own housing 130. This arrangement permits the sensor, sensing fluid and microneedles to be discarded after a period of use (e.g., when reservoir 118 is depleted) while enabling the electronics and actuator to be reused. A flexible covering (made, e.g., of polyester or other

plastic-like material) may surround and support the disposable components. In particular, the interface between actuator 120 and reservoir 118 must permit actuator 120 to move sensing fluid out of reservoir 118, such as by deforming a wall of the reservoir. In these embodiments, housings 128 and 130 may have a mechanical connection, such as a snap or interference fit.

[0039] Figure 2 shows an exploded view of another embodiment of the invention. This figure shows a removable seal 203 covering the sharp distal ends of microneedles 202 and attached, e.g., by adhesive. Seal 203 maintains the sensing fluid within the microneedles and sensing area prior to use and is removed prior to placing the glucose monitor 200 on the skin using adhesive pressure seal 216. In this embodiment, microneedles 202, sensing fluid and waste reservoirs 218 and 226, sensing microchannel 208 and electrochemical glucose sensor 212 are contained within and/or supported by a housing 228 which forms the disposable portion of the device. A second housing 230 supports an electronics board 214 (containing, e.g., processing circuitry, a power source, transmission circuitry, etc.) and an actuator 220 that can be used to move sensing fluid out of reservoir 218, through microchannel 208 into waste reservoir 226. Electrical contacts 215 extend from electronics board 214 to make contact with corresponding electrodes in glucose sensor 212 when the device is assembled.

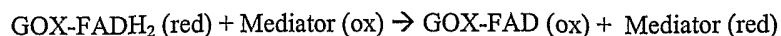
[0040] The following is a description of glucose sensors that may be used with the glucose monitors of this invention. In 1962 Clark and Lyons proposed the first enzyme electrode (that was implemented later by Updike and Hicks) to determine glucose concentration in a sample by combining the specificity of a biological system with the simplicity and sensitivity of an electrochemical transducer. The most common strategies for glucose detection are based on using either glucose oxidase or glucose dehydrogenase enzyme.

[0041] Electrochemical sensors for glucose, based on the specific glucose oxidizing enzyme glucose oxidase, have generated considerable interest. Several commercial devices based on this principle have been developed and are widely used currently for monitoring of glucose, e.g., self testing by patients at home, as well as testing in physician offices and hospitals. The earliest amperometric glucose biosensors were based on glucose oxidase (GOX) which generates hydrogen peroxide in the presence of oxygen and glucose according to the following reaction scheme:



[0042] Electrochemical biosensors are used for glucose detection because of their high sensitivity, selectivity and low cost. In principal, amperometric detection is based on measuring either the oxidation or reduction of an electroactive compound at a working electrode (sensor). A constant potential is applied to that working electrode with respect to another electrode used as the reference electrode. The glucose oxidase enzyme is first reduced in the process but is reoxidized again to its active form by the presence of any oxygen resulting in the formation of hydrogen peroxide. Glucose sensors generally have been designed by monitoring either the hydrogen peroxide formation or the oxygen consumption. The hydrogen peroxide produced is easily detected at a potential of +0.6 V relative to a reference electrode such as an Ag/AgCl electrode. However, sensors based on hydrogen peroxide detection are subject to electrochemical interference by the presence of other oxidizable species in clinical samples such as blood or serum. On the other hand, biosensors based on oxygen consumption are affected by the variation of oxygen concentration in ambient air. In order to overcome these drawbacks, different strategies have been developed and adopted.

[0043] Selectively permeable membranes or polymer films have been used to suppress or minimize interference from endogenous electroactive species in biological samples. Another strategy to solve these problems is to replace oxygen with electrochemical mediators to reoxidize the enzyme. Mediators are electrochemically active compounds that can reoxidize the enzyme (glucose oxidase) and then be reoxidized at the working electrode as shown below:



[0044] Organic conducting salts, ferrocene and ferrocene derivatives, ferricyanide, quinones, and viologens are considered good examples of such mediators. Such electrochemical mediators act as redox couples to shuttle electrons between the enzyme and electrode surface. Because mediators can be detected at lower oxidation potentials than that used for the detection of hydrogen peroxide the interference from electroactive species (e.g., ascorbic and uric acids present) in clinical samples such as blood or serum is greatly reduced. For example ferrocene derivatives have oxidation potentials in the +0.1 to 0.4 V range. Conductive organic salts such as tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ) can operate as low as 0.0 Volts relative to a Ag/AgCl reference electrode. Nankai et al, WO 86/07632, published Dec. 31, 1986, discloses an amperometric biosensor system in which a fluid containing glucose is contacted with glucose oxidase and potassium ferricyanide. The glucose is oxidized and the ferricyanide is reduced to ferrocyanide. This reaction is catalyzed by glucose oxidase. After two minutes, an electrical potential is applied, and a current caused by the re-oxidation of the ferrocyanide to ferricyanide is obtained. The current value, obtained a few seconds after the potential is applied, correlates to the concentration of glucose in the fluid.

[0045] There are multiple glucose sensors that may be used with this invention. In a three electrode system, shown in Figure 3(a), a working electrode 302 is referenced against a reference electrode 304 (such as Ag/AgCl) and a counter electrode 306 (such as Pt) provides a means for current flow. The three electrodes are mounted on a substrate 308, then covered with a reagent 310, as shown in Figure 3(b).

[0046] Figure 4 shows a two electrode system, wherein the working and counter electrodes 402 and 404 are made of different electrically conducting materials. Like the embodiment of Figure 3, the electrodes 402 and 404 are mounted on a flexible substrate 408 as shown in Figure 4(a) and covered with a reagent 410, as shown in Figure 4(b). In an alternative two electrode system, the working and counter electrodes are made of the same electrically conducting materials, where the reagent exposed surface area of the counter electrode is slightly larger than that of the working electrode or where both the working and counter electrodes are substantially of equal dimensions.

[0047] In amperometric and coulometric biosensors, immobilization of the enzymes is also very important. Conventional methods of enzyme immobilization include covalent binding, physical adsorption or cross-linking to a suitable matrix may be used.

[0048] In some embodiments, the reagent is contained in a reagent well in the biosensor. The reagent includes a redox mediator, an enzyme, and a buffer, and covers substantially equal surface areas of portions of the working and counter electrodes. When a sample containing the analyte to be measured, in this case glucose, comes into contact with the glucose biosensor the analyte is oxidized, and simultaneously the mediator is reduced. After the reaction is complete, an electrical potential difference is applied between the electrodes. In general the amount of oxidized form of the redox mediator at the counter electrode and the applied potential difference must be sufficient to cause diffusion limited electrooxidation of the reduced form of the redox mediator at the surface of the working electrode. After a short time delay, the current produced by the electrooxidation of the reduced form of the redox mediator is measured and correlated to the amount of the analyte concentration in the sample. In some cases, the analyte sought to be measured may be reduced and the redox mediator may be oxidized.

[0049] In the present invention, these requirements are satisfied by employing a readily reversible redox mediator and using a reagent with the oxidized form of the redox mediator in an amount sufficient to insure that the diffusion current produced is limited by the oxidation of the reduced form of the redox mediator at the working electrode surface. For current produced during electrooxidation to be limited by the oxidation of the reduced form of the redox mediator at the working electrode surface, the amount of the oxidized form of the redox mediator at the surface of

the counter electrode must always exceed the amount of the reduced form of the redox mediator at the surface of the working electrode. Importantly, when the reagent includes an excess of the oxidized form of the redox mediator, as described below, the working and counter electrodes may be substantially the same size or unequal size as well as made of the same or different electrically conducting material or different conducting materials. From a cost perspective the ability to utilize electrodes that are fabricated from substantially the same material represents an important advantage for inexpensive biosensors.

[0050] As explained above, the redox mediator must be readily reversible, and the oxidized form of the redox mediator must be of sufficient type to receive at least one electron from the reaction involving enzyme, analyte, and oxidized form of the redox mediator. For example, when glucose is the analyte to be measured and glucose oxidase is the enzyme, ferricyanide or quinone may be the oxidized form of the redox mediator. Other examples of enzymes and redox mediators (oxidized form) that may be used in measuring particular analytes by the present invention are ferrocene and or ferrocene derivative, ferricyanide, and viologens. Buffers may be used to provide a preferred pH range from about 4 to 8. The most preferred pH range is from about 6 to 7. The most preferred buffer is phosphate (e.g., potassium phosphate) from about 0.1M to 0.5M and preferably about 0.4M. (These concentration ranges refer to the reagent composition before it is dried onto the electrode surfaces.) More details regarding glucose sensor chemistry and operation may be found in: Clark LC, and Lyons C, "Electrode Systems for Continuous Monitoring in Cardiovascular Surgery," Ann NY Acad Sci, 102:29, 1962; Updike SJ, and Hicks GP, "The Enzyme Electrode," Nature, 214:986, 1967; Cass, A.E. G., G. Davis. G.D. Francis, et. al. 1984. Ferrocene-mediated enzyme electrode for amperometric determination of glucose. Anal.Chem. 56:667-671; and Boutelle, M.G.,C. Stanford. M. Fillenz, et.al. 1986. An amperometric enzyme electrode for monitoring brain glucose in the freely moving rat. Neurosci lett. 72:283-288.

[0051] Another embodiment of the disposable portion of the glucose monitor invention is shown in **Figure 5** with a microneedle array **502** and a glucose sensor **512** in fluid communication with a sensing area in channel **508**. In this embodiment, actuator **520** is on the side of sensing fluid reservoir **518**, and the waste reservoir **526** is expandable. Operation of actuator **520** sends sensing fluid from reservoir **518** through one way flap valve **522** into the sensing area in channel **508** and forces sensing fluid within channel **508** through flap valve **524** into the expandable waste reservoir **526**.

[0052] In the embodiment of **Figure 5** (and potentially other embodiments), the starting amount of sensing fluid in the calibration reservoir **518** is about 1.0 ml or less, and operation of the sensing fluid actuator **520** sends a few microliters (e.g., 10 μ L) of sensing fluid into channel **508**. Recalibrating the device three times a day for seven days will use less than 250 μ L of sensing fluid.

[0053] **Figures 6 and 7** show a remote receiver for use with a glucose monitoring system. The wireless receiver can be configured to be worn by a patient on a belt, or carried in a pocket or purse. In this embodiment, glucose sensor information is transmitted by the glucose sensor **602** applied to the user's skin to receiver **600** using, e.g., wireless communication such as radio frequency (RF) or Bluetooth wireless. The receiver may maintain a continuous link with the sensor, or it may periodically receive information from the sensor. The sensor and its receiver may be synchronized using RFID technology or other unique identifiers. Receiver **600** may be provided with a display **604** and user controls **606**. The display may show, e.g., glucose values, directional glucose trend arrows and rates of change of glucose concentration. The receiver can also be configured with a speaker adapted to deliver an audible alarm, such as high and low glucose alarms. Additionally, the receiver can include a memory device, such as a chip, that is capable of storing glucose data for analysis by the user or by a health care provider.

[0054] In some embodiments, the source reservoir for the calibration and sensing fluid may be in a blister pack which maintains its integrity until punctured or broken. The actuator may be a small syringe or pump. Use of the actuator for recalibration of the sensor may be performed manually by the user or may be performed automatically by the device if programmed accordingly. There may also be a spring or other loading mechanism within the reusable housing that can be activated to push the disposable portion—and specifically the microneedles—downward into the user's skin.

[0055] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention.

It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A glucose monitor comprising
a plurality of tissue piercing elements, each tissue piercing element comprising a distal opening, a
5 proximal opening and an interior space extending between the distal and proximal openings;
a sensing area in fluid communication with the proximal openings of the tissue piercing elements;
sensing fluid extending from the sensing area into substantially the entire interior space of the
tissue piercing elements; and
a glucose sensor adapted to detect a concentration of glucose in the sensing fluid within the
10 sensing area.
2. The glucose monitor of claim 1 further comprising a removable cover extending over the distal
openings of the tissue piercing elements.
3. The glucose monitor of claim 1 further comprising a display adapted to display a glucose
concentration sensed by the sensor.
- 15 4. The glucose monitor of claim 3 wherein the display is disposed in a housing separate from the
sensor, the glucose monitor further comprising a communicator adapted to wirelessly communicate sensor
information from the sensor to the display.
5. The glucose monitor of claim 1 further comprising a sensing fluid reservoir and a pump adapted to
move sensing fluid out of the sensing fluid reservoir into the sensing area.
- 20 6. The glucose monitor of claim 5 wherein the pump comprises a manual actuator.
7. The glucose monitor of claim 5 further comprising a waste reservoir adapted to receive sensing
fluid from the sensing area.
8. The glucose monitor of claim 7 further comprising a housing comprising a first part and a second
part, the first part of the housing being adapted to support the tissue piercing elements, the sensing fluid reservoir,
25 the sensing area, and at least part of the sensor, the second part of the housing comprising an electrical connection to
the at least part of the sensor in the first part of the housing, the housing further comprising a connector adapted to
connect and disconnect the first part of the housing from the second part of the housing.
9. The glucose monitor of claim 8 wherein the first part of the housing is further adapted to support
the pump.
- 30 10. The glucose monitor of claim 8 wherein the first part of the housing is further adapted to support
the waste reservoir.
11. The glucose monitor of claim 8 further comprising a communicator supported by the second part
of the housing and adapted to communicate sensor information to a display.

12. The glucose monitor of claim 5 wherein the sensing fluid in the sensing fluid reservoir has a glucose concentration of between about 0 mg/dl and about 400 mg/dl.

13. The glucose monitor of claim 1 further comprising an adhesive element adjacent the tissue piercing elements and adapted to attach to a user's skin.

5 14. The glucose monitor of claim 1 wherein the glucose sensor, tissue piercing elements and sensing area are further adapted to detect a concentration of glucose in the sensing fluid within the sensing area without extracting interstitial fluid through the distal openings into the interior space.

15. A method of in vivo monitoring of an individual's interstitial fluid glucose concentration comprising:

10 inserting distal ends of a plurality of tissue piercing elements through a stratum corneum area of the individual's skin, the tissue piercing elements each comprising a distal opening, a proximal opening, an interior space extending between the distal and proximal openings, and a sensing fluid filling substantially the entire interior space; and
sensing a glucose concentration of the sensing fluid.

15 16. The method of claim 15 further comprising removing a cover from the distal openings of the tissue piercing elements prior to the inserting step.

17. The method of claim 15 further comprising displaying glucose concentration information remote from the stratum corneum area of the individual's skin.

20 18. The method of claim 17 further comprising wirelessly communicating glucose concentration information to a display.

19. The method of claim 15 wherein the sensing step is performed by a sensor in fluid communication with a sensing area and the interior spaces of the tissue piercing elements, the method further comprising calibrating the sensor by moving sensing fluid into the sensing area.

25 20. The method of claim 19 further comprising moving sensing fluid out of the sensing area as sensing fluid is moved into the sensing area.

21. The method of claim 19 wherein the step of moving sensing fluid comprises operating a pump.

22. The method of claim 19 wherein the step of moving sensing fluid comprises moving sensing fluid having a glucose concentration of between about 0 mg/dl and about 400 mg/dl.

30 23. The method of claim 19 wherein the step of moving sensing fluid comprises moving sensing fluid from a sensing fluid reservoir, the sensing fluid reservoir, sensing area, tissue piercing elements and at least part of the sensor being supported by a first part of a housing, the method further comprising attaching the first part of the housing to a second part of the housing prior to the inserting step, the second part of the housing comprising an electrical connection to the at least part of the sensor in the first part of the housing.

24. The method of claim 23 further comprising separating the second part of the housing from the first part of the housing after the sensing step.

25. The method of claim 15 further comprising attaching the tissue piercing elements to the individual with adhesive.

5 26. The method of claim 15 further comprising permitting glucose to diffuse from interstitial fluid of the individual into the sensing area without extracting interstitial fluid through the distal openings into the interior space.

27. A glucose monitor comprising

10 a plurality of tissue piercing elements, each tissue piercing element comprising a distal opening, a proximal opening and an interior space extending between the distal and proximal openings;

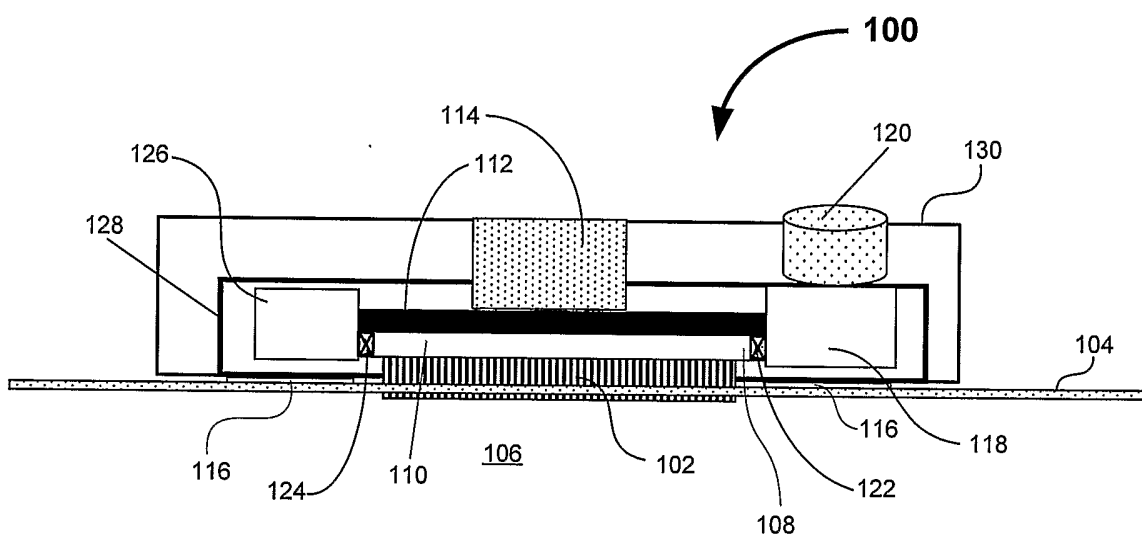
 a sensing area in continuous fluid communication with the proximal openings of the tissue piercing elements;

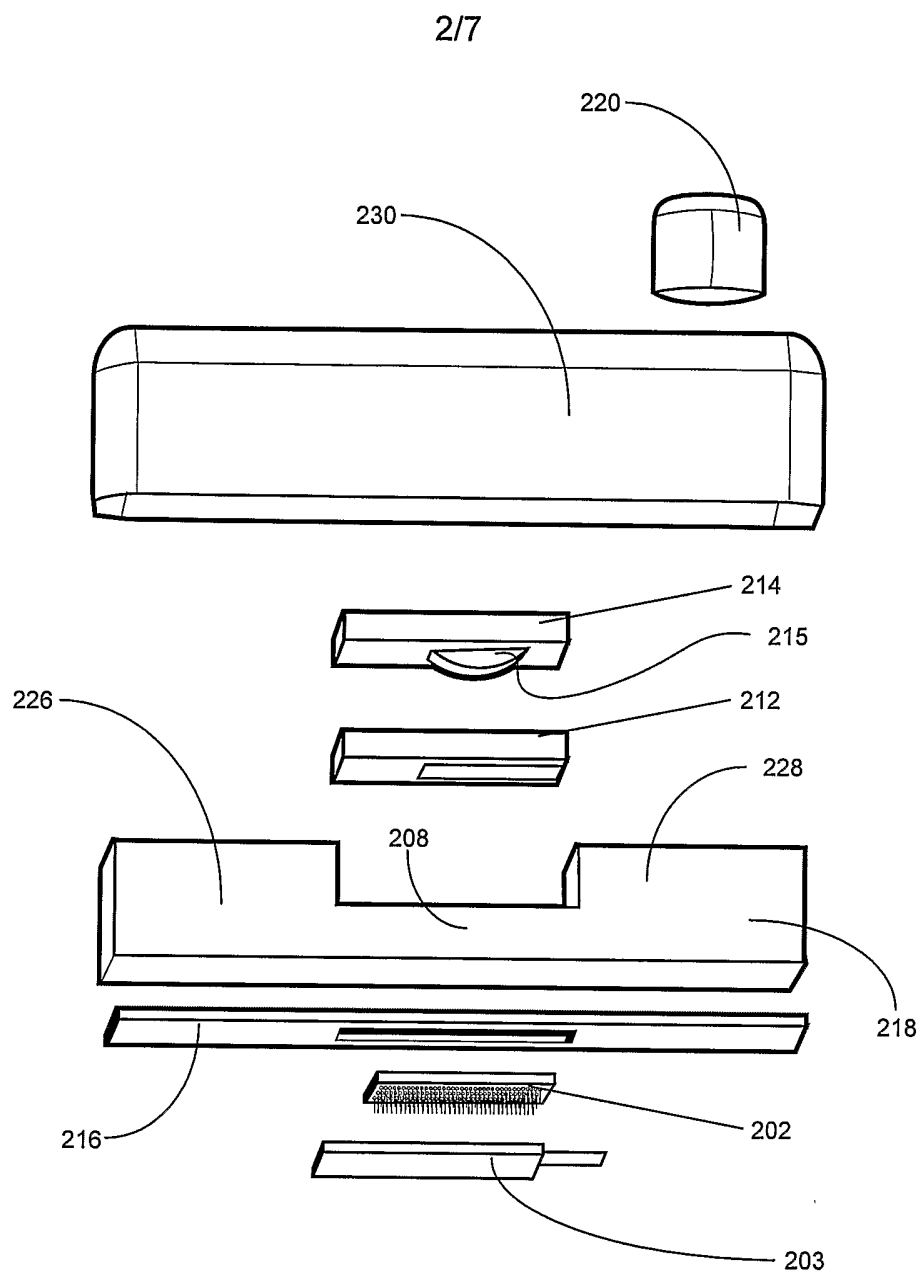
 sensing fluid extending from the sensing area into substantially the entire interior space of the tissue piercing elements; and

15 a glucose sensor adapted to continuously detect a concentration of glucose in the sensing fluid within the sensing area

 and further adapted to be self-calibrating.

1/7

**Figure 1**

**Figure 2**

3/7

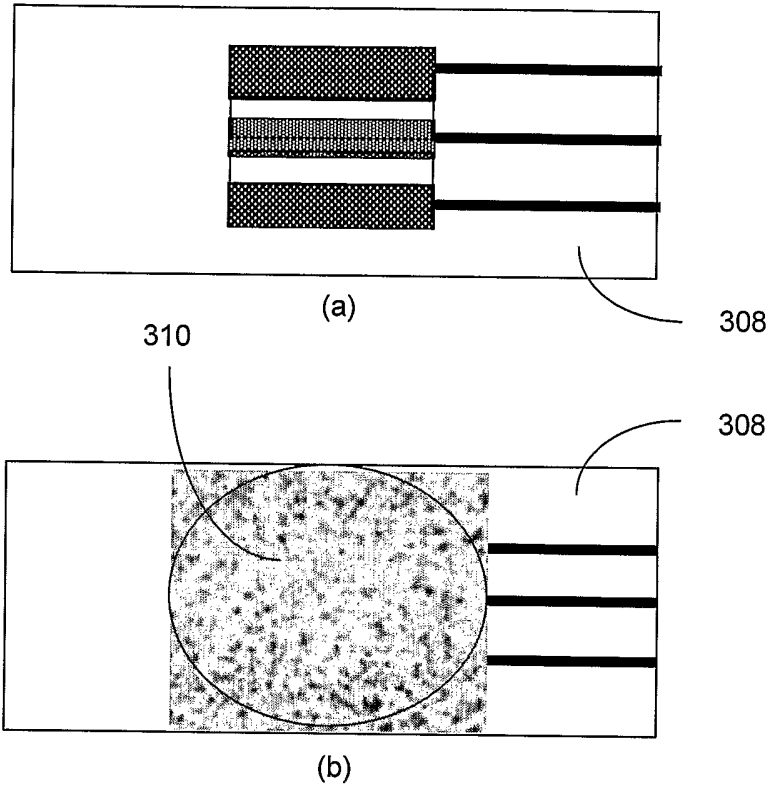
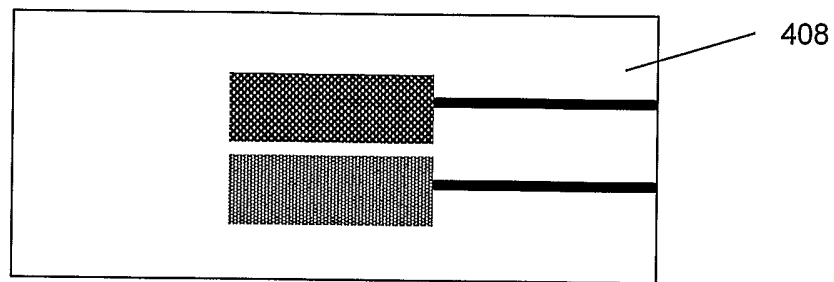
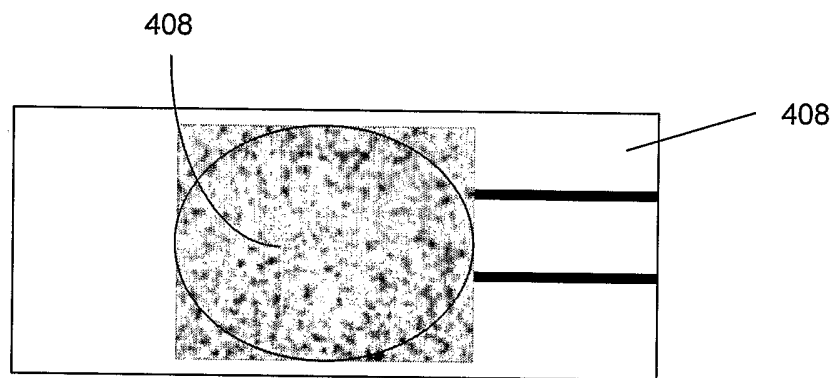


Figure 3

4/7



(a)



(b)

Figure 4

5/7

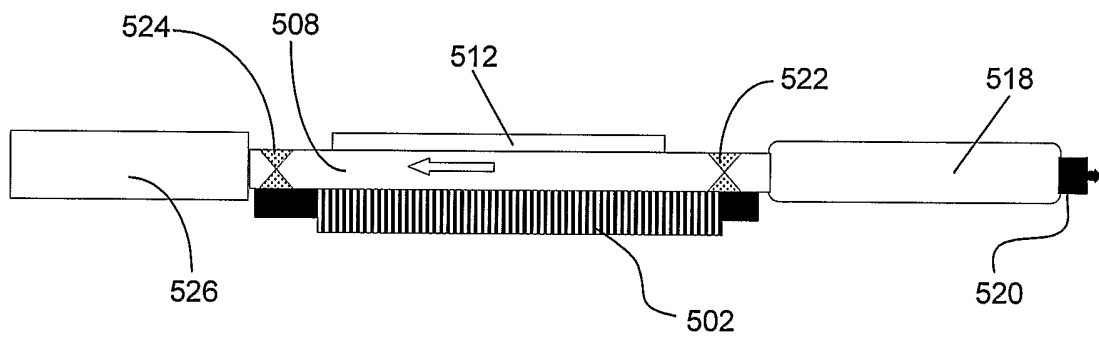


Figure 5

6/7

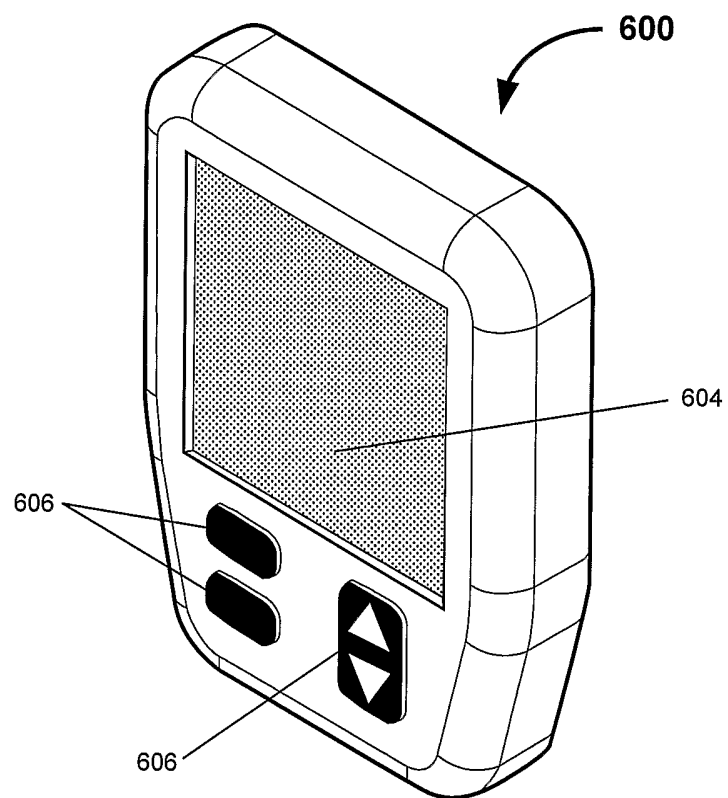


Figure 6

7/7

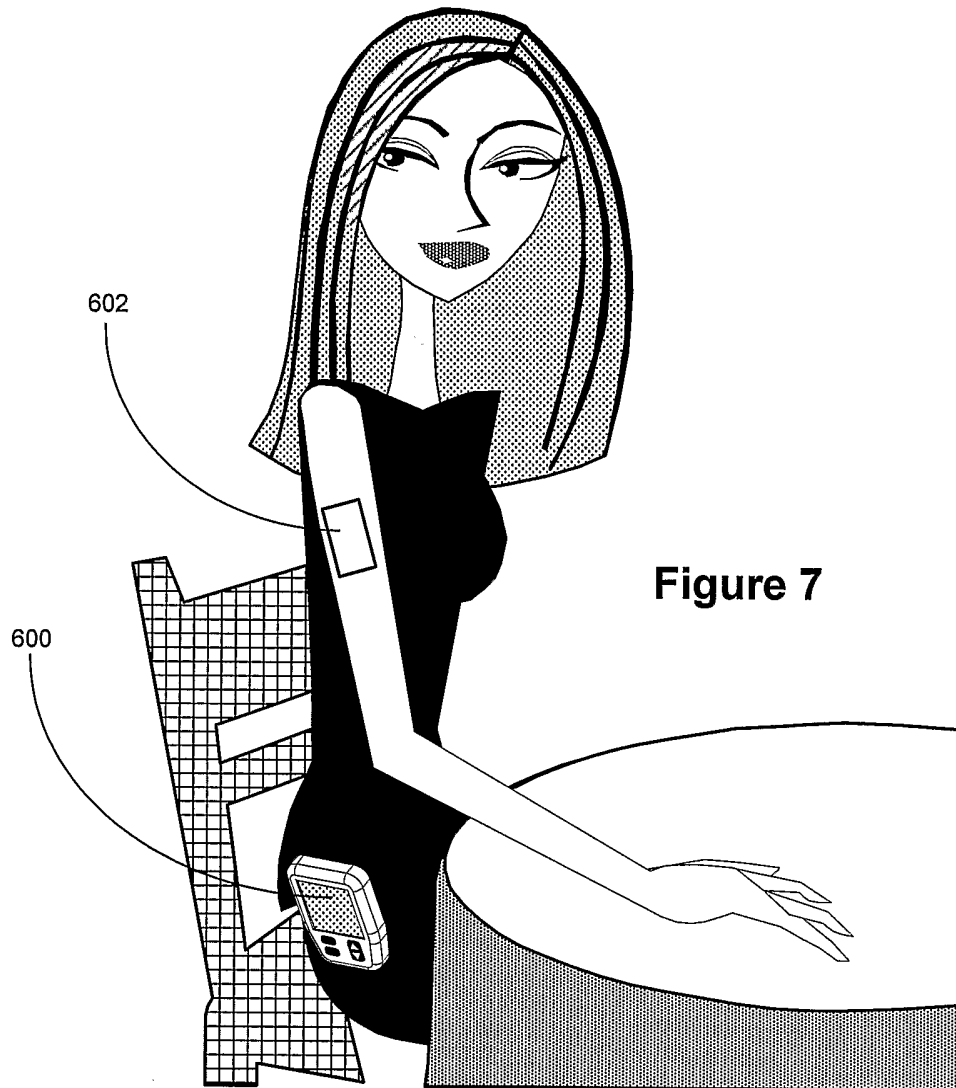


Figure 7