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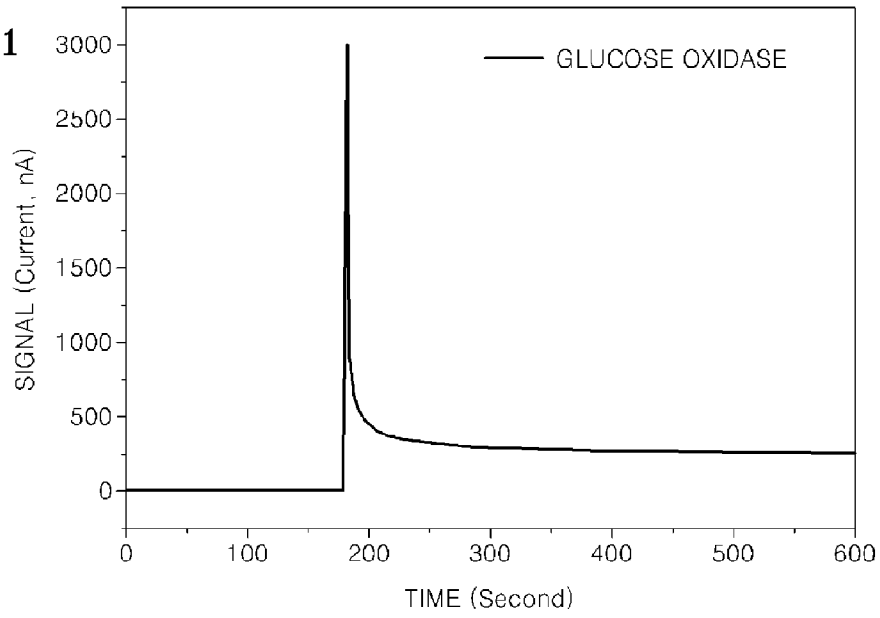
(54) Title: DEVICE FOR MEASURING GLUCOSE CONCENTRATION AND METHOD OF MEASURING GLUCOSE CONCENTRATION USING THE SAME

FIG. 1



(57) Abstract: Provided are a reverse iontophoresis device for measuring a body glucose concentration including: a first sensor unit including an ion conductive medium including a glucose oxidase, an extraction electrode electrically connected to the ion conductive medium, a working electrode, a counter electrode and a reference electrode; and a second sensor unit including the same structure as the first sensor unit except for including an ion conductive medium without the glucose oxidase, wherein the glucose concentration is calibrated by subtracting an interference signal value measured by the second sensor unit from a glucose concentration value measured by the first sensor unit, and a method of measuring the glucose concentration.

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Description

Device for measuring glucose concentration and method of Measuring glucose concentration using the same

Technical Field

[1] The present invention relates to a reverse iontophoresis device for measuring a glucose concentration and a method of measuring a glucose concentration using the same.

Background Art

[2] A non-invasive glucose monitoring device using an iontophoresis and a patch for extracting glucose employed in the device have been disclosed. For example, Korean Patent Publication No. 1999-0077833 discloses a sampling system monitoring a concentration of a substance in a biological system, the sampling system including a storage unit including an ion conductive medium and an enzyme which reacts with the substance to produce hydrogen peroxide, a sampling means operably contacting with the storage unit and extracting the substance to the storage unit until the concentration of the substance is a sub-milimolar scale, and a sensor element comprising, a sensing electrode that reacts electrochemically with hydrogen peroxide to provide a detectable signal, said sensing electrode comprising a platinum-group metal, a geometric surface area that ranges from about 0.1 to about 3 cm^2, a background current that ranges from about 2 to about 60 nA or less when measured in a buffer solution at 0.6V, and a sensitivity of at least about 6 to about 180 nA/μM of hydrogen peroxide when measured in a buffer solution at 0.6V. In addition, Korean Patent Publication No. 2005-0026791 discloses an electrode assembly of a non-invasive glucose monitoring device including an ion conductive contact unit which contacts with the skin, an electrode assembly provided to the opposite side of the ion conductive contact unit, a unit measuring the amount of electricity and electrically connected to the electrode, and a monitoring unit connected to the unit measuring the amount of electricity, the electrode assembly comprising: a working electrode to which a voltage for measuring blood glucose level is applied, a first extraction electrode surrounding most part of the working electrode to which a current is applied to extract glucose in body fluids through the skin, a counter electrode surrounding most part of the extraction electrode and electrically connected to the working electrode through the ion conductive contact unit, an analysis unit formed at a peripheral portion of the extraction electrode to which the counter electrode does not extend and including the working electrode and a reference potential electrode, and an extraction unit separated from the analysis unit and including a second extraction electrode which applies an extraction current to the

skin with the first extraction electrode of the analysis unit. Glucose stored in the ion conductive contact unit, for example a hydrogel, reacts with a glucose oxidase immobilized on the surface of the hydrogel or in the hydrogel to produce hydrogen peroxide. The hydrogen peroxide is oxidized by the voltage applied between the working electrode and the reference electrode to generate a current. FIG. 1 is a graph illustrating change in the amount of electricity generated from glucose extracted by a conventional reverse iontophoresis device. The detected amount of the current is converted to a glucose concentration through algorithms using the area of the current.

[3] In a conventional non-invasive device for measuring blood glucose level and a patch for extracting glucose used in the method, signals are inaccurate and less sensible since they are influenced by changes in moisture content of an ion conductive medium, pressure, temperature and contact resistance in a sensor which may caused by interference substances and extrinsic factors that can be extracted during the glucose extraction through skin. Changes in the moisture content of an ion conductive medium, pressure, temperature and contact resistance in a sensor may be influenced by movements of an individual, food intake, the degree of stress and body temperature change, and the like, but the causes are not limited thereto. Thus, in the conventional device for measuring a glucose concentration and method of measuring the glucose concentration using the device, interference signals caused by interference substances and other extrinsic factors need to be calibrated.

Disclosure of Invention

Technical Problem

[4] The present invention provides a reverse iontophoresis device for measuring a glucose concentration that can accurately measure the glucose concentration by calibrating changes in the amount of electricity caused by interference substances and extrinsic factors.

[5] The present invention also provides a method of measuring a body glucose concentration using the reverse iontophoresis device for measuring a glucose concentration.

Technical Solution

[6] Hereinafter, the present invention will now be described more fully with reference to the accompanying drawings, in which exemplary embodiments of the invention are shown.

[7] The present invention provides a reverse iontophoresis device for measuring a body glucose concentration including: a first sensor unit including an ion conductive medium having a glucose oxidase, and an extraction electrode electrically connected to the ion conductive medium, a working electrode, a counter electrode and a reference

electrode; and a second sensor unit including the same structure as the first sensor unit except for including an ion conductive medium without the glucose oxidase,

[8] wherein the glucose concentration is calibrated by subtracting an interference signal value measured by the second sensor unit from a glucose concentration value measured by the first sensor unit.

[9] The 'reverse iontophoresis' used herein is a technique for extraction of a substance through a skin by applying an electric field to the surface of the skin. Such a reverse iontophoresis is well known in the art. For example, a method of using a reverse iontophoresis in order to extract ionic species (Na+, K+) through the surface of the skin is disclosed by Benjamin et al. (1954) J. Appl. Physiol. 6:401. A method of applying a reverse iontophoresis to extraction of various substances through the surface of the skin is disclosed by Glikfeld et al. (1989) Pharma. Engineering and Computing 16(2):125; and Burnette, R. and Marrero, D. (1986) J. Pharm. Sci. 75(8); 738. In addition, a reverse iontophoresis device is well known in the art. For example, Korean Patent Publication Nos. 1999-0077833 and 2005-0026791, and U.S. Patent No. 5,954,685 disclose reverse iontophoresis devices. It will be understood that a reverse iontophoresis device according to the present invention has configurations commonly used in a conventional reverse iontophoresis device except for configurations described herein.

[10] Here, the ion conductive medium may be any medium that can transfer ionic substances when a current is applied thereto. The ion conductive medium may be a conductive polymer gel and a hydrophilic polymer gel, and preferably an ion conductive hydrophilic polymer gel. The ion conductive medium may be any medium that has a surface contacting with the skin, and can be electrically connected to an extraction electrode for extracting glucose from interstitial fluids by a reverse iontophoresis and a detection electrode for detecting the extracted glucose.

[11] An enzyme included in the ion conductive medium may be any enzyme that reacts with glucose and generates a chemical signal, and preferably a glucose oxidase. The chemical signal may be substances derived from glucose by the enzyme or derivatives thereof. For example, the chemical signal may be hydrogen peroxide. The enzyme may be included in one of the ion conductive mediums.

[12] The glucose oxidase may be homogenously dispersed in the ion conductive medium. In addition, the glucose oxide may be homogenously coated on the surface of the ion conductive medium.

[13] The working electrode, the counter electrode and the reference electrode function as detection electrodes that detect electrical signals generated by electrochemically oxidizing hydrogen peroxide which is resulted from the reaction of glucose extracted from interstitial fluids in the skin by a reverse iontophoresis and stored in the ion

conductive medium with a glucose oxidase immobilized in the ion conductive medium.

[14] The 'electrode' used herein is a part of an electrochemical cell through which an electric current passes by moving electrons when it is in contact with an electrolyte. The electrode which is essential of all of galvanic cells and electrolytic cells may be formed of an electrically conductive material such as Ag, Pb, Zn, Al, Co, Fe, Ni, Hg, graphite, Au, or Pt, an oxide thereof, and an alloy thereof.

[15] The 'extraction electrode' used herein is an electrode to which a sufficient amount of current is applied so that body substances can be extracted by a reverse iontophoresis through the skin. When a current is applied to the extraction electrode, the direction of the current in the extraction electrode may be alternated at predetermined intervals. An extraction of glucose and measurement of the signals generated from the glucose may be achieved in a predetermined period within each interval of the change of the current direction, respectively. For example, glucose can be extracted for 3 minutes by using the extraction eletrode and the signals can be generated for 7 minutes by using the working electrode from the extracted glucose, in each interval of the change of current direction. The 'counter electrode' used herein is an electrode used in an electrochemical cell functioning to apply a constant voltage to a working electrode and a reference electrode. The 'reference electrode' used herein is an electrode providing a reference potential. The 'working electrode' used herein is an electrode measuring the amount of a current generated by oxidation-reduction with the substances by the applied voltage. In the reverse iontophoresis device, the extraction electrode, the working electrode, the counter electrode and the reference electrode may be: an electrode formed of Pt, Au and Ag; the electrode further including C; or a Ag/AgCl electrode, but materials that are used to form the electrodes are not limited thereto. Those electrodes may be prepared on a substrate using a known method in the art such as screen printing, sputtering, or the like.

[16] A reverse iontophoresis device for measuring a body glucose concentration according to the present invention provides a calibrated glucose concentration by subtracting an interference signal value measured by the second sensor unit from a glucose concentration value measured by the first sensor unit. Since the ion conductive medium of the first sensor unit includes a glucose oxidase, the current derived from the oxidation of hydrogen peroxide generated from reacting extracted glucose with a glucose oxidase is derived from glucose and other interference substances. Since an ion conductive medium of the second sensor unit does not include a glucose oxidase, the current is derived from other interference substances except for glucose. Thus, a current value obtained by subtracting the current measured by the second sensor unit from the current measured by the first sensor unit is a current derived only from glucose concentration by eliminating the interference signal value. A process of cal-

ibrating the glucose concentration may be performed by a microprocessor or a program including algorithms performing the calculation.

[17] According to an embodiment of the present invention, the ion conductive medium of the reverse iontophoresis device is a hydrogel, and the extraction electrode is in the shape of a disconnected ring, the working electrode is a circle formed inside of the extraction electrode, and the counter electrode and the reference electrode are parts of a ring surrounding the extraction electrode in the first and second sensor units. However, the structures of those electrodes in the reverse iontophoresis device are not limited thereto.

[18] In the reverse iontophoresis device of the present invention, the glucose concentration is obtained in the following process. A current is applied to each extraction electrode of the first and second sensor units for a predetermined period of time while the ion conductive medium is attached to the skin of an individual, and an opposite current is applied thereto for a predetermined period of time to extract glucose from the extraction electrodes to which a negative current is applied. Then, a current derived from interference signals except for glucose and measured by the working electrode of the second sensor unit is subtracted from a current derived from the oxidation of hydrogen peroxide generated from reacting extracted glucose with a glucose oxidase and measured by the working electrode of the first sensor unit to calibrate the glucose concentration. That is, after a current is applied in a direction, for example, for about 10 minutes, the direction of the current is alternated. An extraction of glucose and measurement of the signals generated from the glucose may be achieved in a predetermined period within each interval of the change of the current direction, respectively. For example, glucose can be extracted for 3 minutes by using the extraction eletrode and the signals can be generated for 7 minutes by using the working electrode from the extracted glucose, in each interval of the change of current direction. When the extraction electrode in the first and second sensor units is a negative electrode, glucose is extracted to the ion conductive medium. Thus, the current measured by the working electrode of the first and second sensor units are values measured at a predetermined time interval. The predetermined time interval may be 1-60 minutes, preferably 1-40 minutes, more preferably 1-20 minutes, most preferably 1-10 minutes.

[19] The present invention also provides a method of measuring a body glucose concentration, the method including:

[20] contacting an ion conductive medium of a first and second sensor units of a reverse iontophoresis device for measuring a body glucose concentration according to the present invention to the skin of an individual;

[21] applying a current to each extraction electrode of the first and second sensor units for a predetermined period of time and applying an opposite current thereto for a prede-

termined period of time to extract glucose to the extraction electrodes to which a negative current is applied; and

[22] measuring current values by each working electrode of the first and second sensor units, and subtracting the current value measured by the working electrode of the second sensor unit from the current value measured by the working electrode of the first sensor unit to obtain a calibrated glucose concentration.

[23] The individual includes a mammal. The mammal may include human, monkey, pig, cow, horse, dog, sheep and cat, but is not limited thereto.

[24] The current may be applied to the extraction electrode of the first and second sensor units using any power supplying means that is widely known in the art . The time for applying the current may be adjusted, for example, the current may be applied for 1-60 minutes, preferably 1-40 minutes, more preferably 1-20 minutes, most preferably 1-10 minutes.

[25] Electrical signals generated from glucose and interference substances in the ion conductive medium may be measured by the working electrode, the counter electrode and the reference electrode. A value obtained by subtracting the current value measured by the working electrode of the second sensor unit from the current value measured by the working electrode of the first sensor unit is a current value derived only from glucose concentration by eliminating the interference signal value. A process of calibrating the glucose concentration may be performed by a micro-processor or a program including algorithms performing the calculation. The calibrated glucose concentration may be obtained by subtracting an area of the current measured by the second sensor unit as shown in a graph from an area of the current measured by the first sensor unit as shown in a graph.

[26] The present invention also provides a reverse iontophoresis device for measuring a body glucose concentration including: a first sensor unit including an ion conductive medium including a glucose oxidase, an extraction electrode electrically connected to the ion conductive medium, a working electrode, a counter electrode and a reference electrode; a second sensor unit including the same structure as the first sensor unit except for including an ion conductive medium without the glucose oxidase, and a third sensor unit an extraction electrode electrically connected to the extraction electrodes of the first and second sensor units, wherein the glucose concentration is calibrated by subtracting an interference signal value measured by the second sensor unit from a glucose concentration value measured by the first sensor unit.

[27] In the reverse iontophoresis device including the first to third sensor units according to the present invention (hereinafter referred to as 'three-sensor device'), the configurations such as the reverse iontophoresis, the electrodes and the first and second sensor units are the same as those of the two-sensor device and described above with

reference to the two-sensor device.

[28] The reverse iontophoresis device including the first to third sensor units according to the present invention further includes a third sensor unit including an extraction electrode compared to the two-sensor device. The third sensor unit may be separated from the first and second sensor units by the same distance. The extraction of glucose may be performed by alternating the direction of the current applied to the extraction electrodes of the first and third sensor units and the second and third sensor units. An extraction of glucose and measurement of the signals generated from the glucose may be achieved in a predetermined period within each interval of the change of the current direction, respectively. For example, glucose can be extracted for 3 minutes by using the extraction eletrode and the signals can be generated for 7 minutes by using the working electrode from the extracted glucose, in each interval of the change of current direction.

[29] In the three-sensor device, the ion conductive medium may be a hydrogel, and the extraction electrode may be in the shape of a disconnected ring, the working electrode may be a circle formed inside of the extraction electrode, and the counter electrode and the reference electrode may be parts of a ring surrounding the extraction electrode in the first and second sensor units, and the extraction electrode of the third sensor unit may be in the shape of a ring, but the electrode structures are not limited thereto.

[30] In the three-sensor device, the glucose concentration is measured by:

[31] applying a current to each extraction electrode of the first and third sensor units, and each extraction electrode of the second and third sensor units for a predetermined period of time while the ion conductive medium is attached to the skin of an individual such that the extraction electrodes of the first and second sensor units have the same direction of the current and then applying an opposite current thereto for a predetermined period of time to extract glucose to the extraction electrodes to which a negative current is applied, and

[32] subtracting a current value measured by the working electrode of the second sensor unit from a current value measured by the working electrode of the first sensor unit to obtain a calibrated glucose concentration.

[33] Since the direction of the current applied to the first and second sensor units is the same, glucose may be simultaneously extracted to the ion conductive mediums of the first and second sensor units, that is, there is no time difference in the glucose extraction between the first sensor unit and the second sensor unit. Thus, a calibrated glucose concentration may be obtained without the time difference.

[34] The present invention also provides a method of measuring a body glucose concentration, the method including:

[35] contacting an ion conductive medium of a first to third sensor units of the reverse

iontophoresis device for measuring a body glucose concentration according to the present invention to the skin of an individual;

[36] applying a current to each extraction electrode of the first and third sensor units, and each extraction electrode of the second and third sensor units for a predetermined period of time such that the extraction electrodes of the first and second sensor units have the same direction of the current and then applying an opposite current thereto for a predetermined period of time to extract glucose to the extraction electrodes to which a negative current is applied; and

[37] measuring current values by each working electrode of the first and second sensor units, and subtracting the current value measured by the working electrode of the second sensor unit from the current value measured by the working electrode of the first sensor unit to obtain a calibrated glucose concentration.

[38] The individual includes a mammal. The mammal may include human, monkey, pig, cow, horse, dog, sheep and cat, but is not limited thereto.

[39] The current may be applied to the extraction electrodes of the first and third sensor units and to the extraction electrodes of the second and third sensor units using any power supplying means that is widely known in the art. The time for applying the current may be adjusted, for example, for 1-60 minutes, preferably 1-40 minutes, more preferably 1-20 minutes, most preferably 1-10 minutes.

[40] Since the direction of the current applied to the first and second sensor units is the same, glucose and interference substances may be simultaneously extracted to the ion conductive medium of the first and second sensor units, that is, there is no time difference in the glucose and interference substance extraction between the first sensor unit and the second sensor unit.

[41] The electrical signals generated from the extracted glucose and interference substances in the ion conductive medium may be measured using the working electrode and the reference electrode. Thus, a current value obtained by subtracting the current value measured by the second sensor unit from the current value measured by the first sensor unit is a current derived only from glucose concentration by eliminating the interference signal value. A process of calibrating the glucose concentration may be performed by a microprocessor or a program including algorithms performing the calculation. The calibrated glucose concentration may be obtained by subtracting an area of the current measured by the second sensor unit as shown in a graph from an area of the current measured by the first sensor unit as shown in a graph.

Advantageous Effects

[42] According to the reverse iontophoresis device for measuring a body glucose concentration according to the present invention, a glucose concentration in which noise signals generated not only by interference substances but also by extrinsic factors are

removed can be obtained.

[43] According to the method of measuring a body glucose concentration according to the present invention, the body glucose concentration can be quickly and accurately measured.

Description of Drawings

[44] The above and other features and advantages of the present invention will become more apparent by describing in detail exemplary embodiments thereof with reference to the attached drawings in which:

[45] FIG. 1 is a graph illustrating changes in the amount of electricity generated from glucose extracted by a conventional reverse iontophoresis device;

[46] FIG. 2 schematically illustrates the structure of electrodes of a conventional reverse iontophoresis device for measuring a body glucose concentration including two sensor units;

[47] FIGS. 3A and 3B are graphs illustrating signals measured by a first sensor unit of the reverse iontophoresis device of FIG. 2;

[48] FIG. 4 schematically illustrates the structure of electrodes of a reverse iontophoresis device for measuring a body glucose concentration including two sensor units according to an embodiment of the present invention;

[49] FIG. 5 is a graph illustrating interference signal values generated from interference substances measured by a second sensor unit;

[50] FIG. 6 is a graph illustrating signals measured by a first sensor unit and interference signals generated from interference substances measured by the second sensor unit;

[51] FIGS. 7A and 7B schematically illustrate the structure of electrodes of a reverse iontophoresis device for measuring a body glucose concentration including three sensor units according to an embodiment of the present invention; and

[52] FIGS. 8A, 8B and 8C are graphs illustrating signals measured by working electrodes of a first and second sensor units by negatively charging extraction electrodes of the first and second sensor units and positively charging an extraction electrode of a third sensor unit, and applying a constant current to the extraction electrodes for 10 minutes and applying a constant voltage thereto for analysis, and then positively charging the extraction electrodes of the first and second sensor units and negatively charging the extraction electrode of the third sensor unit, and applying the same current and voltage thereto in the reverse iontophoresis device having the structure of electrodes shown in FIG. 7A.

Best Mode

[53] The present invention will now be described in greater detail with reference to the following examples. The following examples are for illustrative purposes only and are

not intended to limit the scope of the invention.

[54] **Examples**

[55] **Comparative Example: Reverse Iontophoresis Device for Measuring Glucose Concentration Including Two Sensor Units and Measurement of Glucose Concentration Using the Same**

[56] A reverse iontophoresis device for measuring a body glucose concentration including two sensor units having the structure of electrodes shown in FIG. 2 was prepared. Then, glucose was extracted from a human individual and the glucose concentration was measured using the reverse iontophoresis device.

[57] FIG. 2 schematically illustrates the structure of electrodes of a conventional reverse iontophoresis device for measuring a body glucose concentration including two sensor units. As shown in FIG. 2, a first sensor unit is consisted of an extraction electrode 10, a working electrode 20, a counter electrode 30 and a reference electrode 40, and a second sensor unit is consisted of only an extraction electrode 10a. Thus, the structure of electrodes of both of the first and second sensor units are different from each other. In addition, the first sensor unit includes an ion conductive medium having a glucose oxidase, but the second sensor unit includes an ion conductive medium not having a glucose oxidase, wherein the ion conductive medium may be electrically connected to the extraction electrode. The ion conductive medium was disposed between the skin and the electrode structure while extracting glucose and measuring the glucose concentration but is not shown in FIG. 2. The conventional reverse iontophoresis device for measuring a body glucose concentration including two sensor units as shown in FIG. 2 may be GluCall™ (KMH Corporation, Korea). In FIG. 2, the second sensor unit simply consisted of the extraction electrode and was used to extract glucose and interference substances. However, since the second sensor did not include electrodes for detecting electrical signals, it could not be used to calibrate interference signals.

[58] Here, the extraction electrode of the first and second sensor units, and the counter electrode and the reference electrode of the first sensor unit were formed of a Ag/AgCl material, and the working electrode of the first sensor unit was formed of a Pt material. Those electrodes were prepared on a polyethylene film which was an insulating material known in the art using screen printing.

[59] FIGS. 3A and 3B are graphs illustrating signals measured by a first sensor unit of the reverse iontophoresis device of FIG. 2. The graphs of FIGS. 3A and 3B illustrate currents measured by the reverse iontophoresis device having the structure of the electrodes as shown in FIG. 2 by the process including negatively charging the extraction electrode 10 of the first sensor unit and positively charging the extraction electrode 10a of the second sensor unit, and applying a current of 0.1 mA to the extraction electrodes for 3 minutes and applying an oxidation potential of 0.4 V thereto

for 7 minutes to extract glucose, and then measuring a current generated by the oxidation of hydrogen peroxide resulted from the reaction of the extracted glucose and the glucose oxidase. The signals shown in FIGS. 3A and 3B indicate signals generated from glucose and other interference substances extracted to the ion conductive medium of the first sensor unit through the skin when the extraction electrode of the first sensor unit was negatively charged. The signals of the interference substances include signals generated from substances oxidized at 0.4 V or less, and signals generated from changes in moisture content, pressure, temperature and contact resistance in the sensor. Here, changes in moisture content, pressure, temperature and contact resistance in the sensor may be caused by movements of an individual, food intake, the degree of stress and body temperature change, and the like, but the causes are not limited thereto.

[60] In FIGS. 3A and 3B, the ion conductive medium of the first sensor unit was an acrylate hydrogel, and the glucose oxidase homogenously dispersed in the hydrogel at the concentration of 200 unit/ml was used. The hydrogel including the glucose oxidase was prepared by radical-polymerizing 2-hydroxypropyl methacrylate (HEMA) and (N,N-dimethylamino) ethylmethacrylate (DMA) in the presence of 200 unit/ml of the glucose oxidase.

[61] As shown in FIGS. 3A and 3B, when glucose is extracted through the skin using the conventional reverse iontophoresis device shown in FIG. 2, signals are inaccurate and less sensible since the signals are also influenced by changes in moisture content of an ion conductive medium, pressure, temperature and contact resistance in a sensor according to extrinsic factors as well as glucose and interference substances. A region indicated by a circle in FIGS. 3A and 3B shows a signal change generated by changes in moisture content of an ion conductive medium, pressure, temperature and contact resistance in a sensor influenced by extrinsic factors.

[62] **Example 1: Reverse Iontophoresis Device for Measuring Glucose Concentration Including Two Sensor Units and Measurement of Glucose Concentration Using the Same**

[63] A reverse iontophoresis device for measuring a body glucose concentration including two sensor units having the structure of electrodes as shown in FIG. 4 was prepared. Then, glucose was extracted from a human individual and the glucose concentration of glucose was measured using the reverse iontophoresis device.

[64] FIG. 4 schematically illustrates the structure of electrodes of a reverse iontophoresis device for measuring a body glucose concentration including two sensor units according to an embodiment of the present invention. As shown in FIG. 4, the electrode structures of the first sensor unit and the second sensor unit were the same except that the ion conductive medium electrically connected to the electrode structure of the first sensor unit included a glucose oxidase but the ion conductive medium of

the second sensor unit did not include a glucose oxidase. The ion conductive medium was disposed between the skin and the electrode structure while extracting glucose and measuring the glucose concentration, but is not shown in FIG. 4. In FIG. 4, reference numerals 10, 20, 30 and 40 respectively indicate an extraction electrode, a working electrode, a counter electrode and a reference electrode of the first sensor unit, and reference numerals 10a, 20a, 30a and 40a respectively indicate an extraction electrode, a working electrode, a counter electrode and a reference electrode of the second sensor unit.

[65] In Example 1, the extraction electrode, the counter electrode and the reference electrode of the first and second sensor units were formed of a Ag/AgCl material, and the working electrode was formed of a Pt material. Those electrodes were prepared on a polyethylene film which is an insulating material known in the art using screen printing.

[66] FIG. 5 is a graph illustrating interference signal values generated from interference substances measured by a second sensor unit. The graph of FIG. 5 illustrates currents measured by the reverse iontophoresis device having the structure of the electrodes as shown in FIG. 4 by the process including positively charging the extraction electrode 10 of the first sensor unit and negatively charging the extraction electrode 10a of the second sensor unit, and applying a current of 0.1 mA to the extraction electrodes for 3 minutes and applying an oxidation potential of 0.4 V thereto for 7 minutess to extract glucose, and then measuring a current generated by the oxidation of hydrogen peroxide resulted from the reaction of the extracted glucose and the glucose oxidase. The signals shown in FIG. 5 indicate signals generated from glucose and other interference substances extracted to the ion conductive medium of the second sensor unit through the skin when the extraction electrode of the second sensor unit was negatively charged. The signals of the interference substances include signals generated from materials oxidized at 0.4 V or less, and signals generated from changes in moisture content of the ion conductive medium, pressure, temperature and contact resistance in the sensor since the ion conductive medium did not include the glucose oxidase. Here, changes in moisture content of the ion conductive medium, pressure, temperature and contact resistance in the sensor may be caused by movements of an individual, food intake, the degree of stress and body temperature change, and the like, but the causes are not limited thereto. On the other hand, signals measured by the working electrode of the first sensor unit include signals generated from the interference signals measured by the working electrode of the second sensor unit and signals generated from the oxidation of glucose. Thus, signals only generated from the glucose concentration without the interference signals can be obtained by subtracting the signals generated from the working electrode of the second sensor unit from the signals generated from

the working electrode of the first sensor unit. In FIG. 5, the ion conductive medium of the first sensor unit was an acrylate hydrogel, and the glucose oxidase homogenously dispersed in the hydrogel at the concentration of 200 unit/ml was used. The hydrogel including the glucose oxidase was prepared by radical-polymerizing 2-hydroxypropyl methacrylate (HEMA) and (N,N-dimethylamino) ethylmethacrylate (DMA) in the presence of 200 unit/ml of the glucose oxidase.

[67] FIG. 6 is a graph illustrating signals measured by a first sensor unit (upper) and interference signals generated from interference substances measured by the second sensor unit (lower). The difference of the areas between the signals measured by the first sensor unit and the signals measured by the second sensor unit in FIG. 6 indicates the signals generated from glucose. The process of extracting glucose and measuring the glucose concentration in FIG. 6 is the same as that described with reference to FIG. 5.

[68] Since glucose forms a complex with a cationic polymer to have a positive charge and is extracted only to the negatively charged extraction electrode, the signal values of the first sensor unit and the signal values of the second sensor unit shown in FIG. 6 has 10 minutes time difference that was taken to change the direction of the current. Thus, if a device for and a method of calibrating the interference signal values as shown in FIGS. 4 to 6 is used, the response time may be delayed although the signal values can be simply calibrated.

[69] **Example 2: Reverse Iontophoresis Device for Measuring Glucose Concentration Including three Sensor Units and Measurement of Glucose Concentration Using the Same**

[70] A reverse iontophoresis device for measuring a body glucose concentration including three sensor units having the structure of electrodes as shown in FIGS. 7A and 7B was prepared. Then, glucose was extracted from a human individual and the glucose concentration of glucose was measured using the reverse iontophoresis device.

[71] FIGS. 7A and 7B schematically illustrate the structure of electrodes of a reverse iontophoresis device for measuring a body glucose concentration including three sensor units according to an embodiment of the present invention. As shown in FIGS. 7A and 7B, the electrode structures of the first sensor unit and the second sensor unit were the same except that the ion conductive medium electrically connected to the electrode structure of the first sensor unit included a glucose oxidase but the ion conductive medium of the second sensor unit did not include a glucose oxidase. The ion conductive medium was disposed between the skin and the electrode structure while extracting glucose and measuring the glucose concentration, but is not shown in FIGS. 7A and 7B. The third sensor unit only included an extraction electrode. In FIGS. 7A and 7B, reference numerals 10, 20, 30 and 40 respectively indicate an extraction

electrode, a working electrode, a counter electrode and a reference electrode of the first sensor unit, reference numerals 10a, 20a, 30a and 40a respectively indicate an extraction electrode, a working electrode, a counter electrode and a reference electrode of the second sensor unit, and the 10b indicates an extraction electrode of the third sensor unit.

[72] The reverse iontophoresis device for measuring a body glucose concentration including three sensor units according to the present invention as shown in FIGS. 7A and 7B may include a program or a microprocessor applying the same directional current to the extraction electrodes of the first and second sensor units when the current is applied to each extraction electrode of the first and third sensor units, and each extraction electrode of the second and third sensor units.

[73] In Example 2, the extraction electrode of the first, second and third sensor units, and the counter electrode and the reference electrode of the first and second sensor units were formed of a Ag/AgCl material, and the working electrode of the first and second sensor units was formed of a Pt material. Those electrodes were prepared on a polyethylene film which is an insulating material known in the art using screen printing.

[74] FIGS. 8A, 8B and 8C illustrate currents measured by the reverse iontophoresis device having the electrode structure of FIG. 7A including negatively charging the extraction electrode 10 of the first sensor unit and the extraction electrode 10a of the second sensor unit and positively charging the extraction electrode 10b of the third sensor unit, and applying a current of 0.1 mA to the extraction electrodes for 3 minutes and applying an oxidation potential of 0.4 V thereto for 7 minutes to extract glucose, and then measuring a current generated by the oxidation of hydrogen peroxide resulted from the reaction of the extracted glucose and the glucose oxidase. FIGS. 8A, 8B and 8C illustrate the results obtained by repeating the process three times in the same conditions.

[75] The signal values of the first and second sensor units shown in FIGS. 8A, 8B and 8C are measured without a time difference during the glucose extraction since the direction of the current applied to the first and second sensor units is the same. The interference signal values measured by the working electrode of the second sensor unit are signal values generated from glucose and other interference substances extracted to the ion conductive medium of the second sensor unit through the skin when the extraction electrode of the second sensor unit is negatively charged. The interference signal values include signals generated from materials oxidized at 0.4 V or less, and signals generated from changes in moisture content, pressure, temperature and contact resistance in the sensor since the ion conductive medium does not include the glucose oxidase. Here, changes in moisture content, pressure, temperature and contact resistance in the sensor may be caused by movements of an individual, food intake, the

degree of stress and body temperature change, and the like, but the causes are not limited thereto. On the other hand, signals measured by the working electrode of the first include signals generated from the interference signal values measured by the working electrode of the second sensor unit and signals generated from the oxidation of glucose. Thus, signals only generated from the glucose concentration without the interference signals can be obtained by subtracting the signals generated from the working electrode of the second sensor unit from the signals generated from the working electrode of the first sensor unit. The region shown as a circle in FIGS. 8A, 8B and 8C indicates an irregular change of the glucose concentration due to the extrinsic factors. Thus, it can be seen the change can be calibrated by subtracting the interference signal values generated from the second sensor unit from the signal values generated from the first sensor unit

[76] In FIGS. 8A, 8B and 8C, the ion conductive medium of the first sensor unit was an acrylate hydrogel, and the glucose oxidase homogenously dispersed in the hydrogel at the concentration of 200 unit/ml was used. The hydrogel including the glucose oxidase was prepared by radical-polymerizing 2-hydroxypropyl methacrylate (HEMA) and (N,N-dimethylamino) ethylmethacrylate (DMA) in the presence of 200 unit/ml of the glucose oxidase.

Industrial Applicability

[77] According to the reverse iontophoresis device for measuring a body glucose concentration according to the present invention, a glucose concentration in which noise signals generated not only by interference substances but also by extrinsic factors are removed can be obtained.

[78] According to the method of measuring a body glucose concentration according to the present invention, the body glucose concentration can be quickly and accurately measured.

Claims

[1] A reverse iontophoresis device for measuring a body glucose concentration comprising: a first sensor unit comprising an ion conductive medium comprising a glucose oxidase, an extraction electrode electrically connected to the ion conductive medium, a working electrode, a counter electrode and a reference electrode; and a second sensor unit comprising the same structure as the first sensor unit except for comprising an ion conductive medium without the glucose oxidase,

wherein the glucose concentration is calibrated by subtracting an interference signal value measured by the second sensor unit from a glucose concentration value measured by the first sensor unit.

[2] The reverse iontophoresis device of claim 1, wherein the ion conductive medium is a hydrogel, and the extraction electrode is in the shape of a disconnected ring, the working electrode is a circle formed inside of the extraction electrode, and the counter electrode and the reference electrode are parts of a ring surrounding the extraction electrode in the first and second sensor units.

[3] The reverse iontophoresis device of claim 1, wherein the glucose concentration is measured by:

applying a current to each extraction electrode of the first and second sensor units for a predetermined period of time and then applying an opposite current thereto for a predetermined period of time while the ion conductive medium is contacted to the skin of an individual to extract glucose to the extraction electrodes to which a negative current is applied; and

subtracting a current value measured by the working electrode of the second sensor unit from a current value measured by the working electrode of the first sensor unit to obtain a calibrated glucose concentration.

[4] The reverse iontophoresis device of claim 1, wherein the glucose oxidase is homogenously dispersed in the ion conductive medium and/or homogenously coated on the surface of the ion conductive medium.

[5] A reverse iontophoresis device for measuring a body glucose concentration comprising:

a first sensor unit comprising an ion conductive medium comprising a glucose oxidase, an extraction electrode electrically connected to the ion conductive medium, a working electrode, a counter electrode and a reference electrode;

a second sensor unit comprising the same structure as the first sensor unit except for comprising an ion conductive medium without the glucose oxidase, and

a third sensor unit comprising an extraction electrode electrically connected to

the extraction electrodes of the first and second sensor units,
wherein the glucose concentration is calibrated by subtracting an interference signal value measured by the second sensor unit from a glucose concentration measured by the first sensor unit.

[6] The reverse iontophoresis device of claim 5, wherein the ion conductive medium is a hydrogel, and the extraction electrode is in the shape of a disconnected ring, the working electrode is a circle formed inside of the extraction electrode, and the counter electrode and the reference electrode are parts of a ring surrounding the extraction electrode in the first and second sensor units, and the extraction electrode of the third electrode is in the shape of a ring.

[7] The reverse iontophoresis device of claim 5, wherein the glucose concentration is measured by:
applying a current to each extraction electrode of the first and third sensor units, and each extraction electrode of the second and third sensor units for a predetermined period of time such that the extraction electrodes of the first and second sensor units have the same direction of the current and then applying an opposite current thereto for a predetermined period of time while the ion conductive medium is contacted to the skin of an individual to extract glucose to the extraction electrodes to which a negative current is applied; and
subtracting a current value measured by the working electrode of the second sensor unit from a current value measured by the working electrode of the first sensor unit to obtain a calibrated glucose concentration.

[8] The reverse iontophoresis device of claim 5, wherein the glucose oxidase is homogenously dispersed in the ion conductive medium and/or homogenously coated on the surface of the ion conductive medium.

[9] A method of measuring a body glucose concentration, the method comprising:
contacting an ion conductive medium of a first and second sensor units of a reverse iontophoresis device for measuring a body glucose concentration according to any one of claims 1 to 4 to the skin of an individual;
applying a current to each extraction electrode of the first and second sensor units for a predetermined period of time and then applying an opposite current thereto for a predetermined period of time to extract glucose to the extraction electrodes to which a negative current is applied; and
measuring current values by each working electrode of the first and second sensor units, and subtracting the current value measured by the working electrode of the second sensor unit from the current value measured by the working electrode of the first sensor unit to obtain a calibrated glucose concentration.

[10] A method of measuring a body glucose concentration, the method comprising:
contacting an ion conductive medium of a first to third sensor units of a reverse iontophoresis device for measuring a body glucose concentration according to any one of claims 5 to 8 to the skin of an individual;
applying a current to each extraction electrode of the first and third sensor units, and each extraction electrode of the second and third sensor units for a predetermined period of time such that the extraction electrodes of the first and second sensor units have the same direction of the current and applying an opposite current thereto for a predetermined period of time to extract glucose to the extraction electrodes to which a negative current is applied; and
measuring current values by each working electrode of the first and second sensor units, and subtracting the current value measured by the working electrode of the second sensor unit from the current value measured by the working electrode of the first sensor unit to obtain a calibrated glucose concentration.

WO 2008/120936 PCT/KR2008/001793

FIG. 1

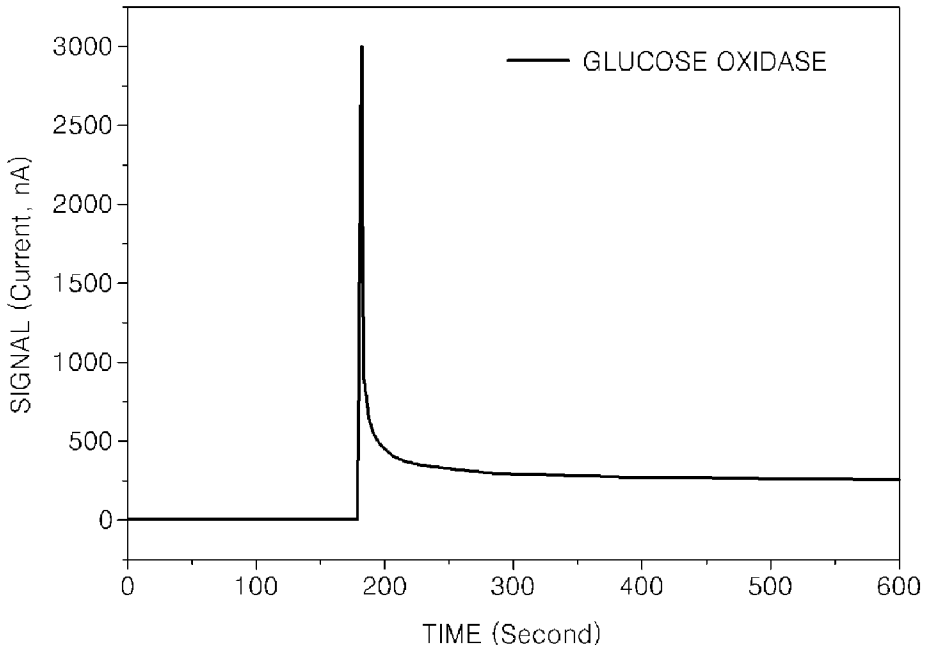


FIG. 2

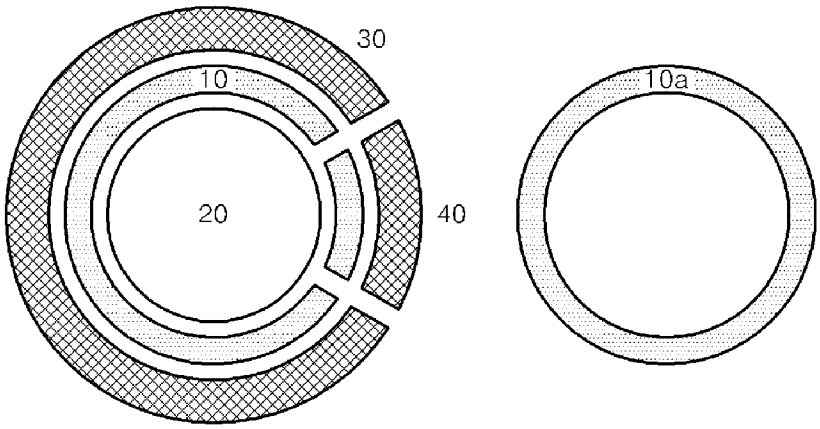
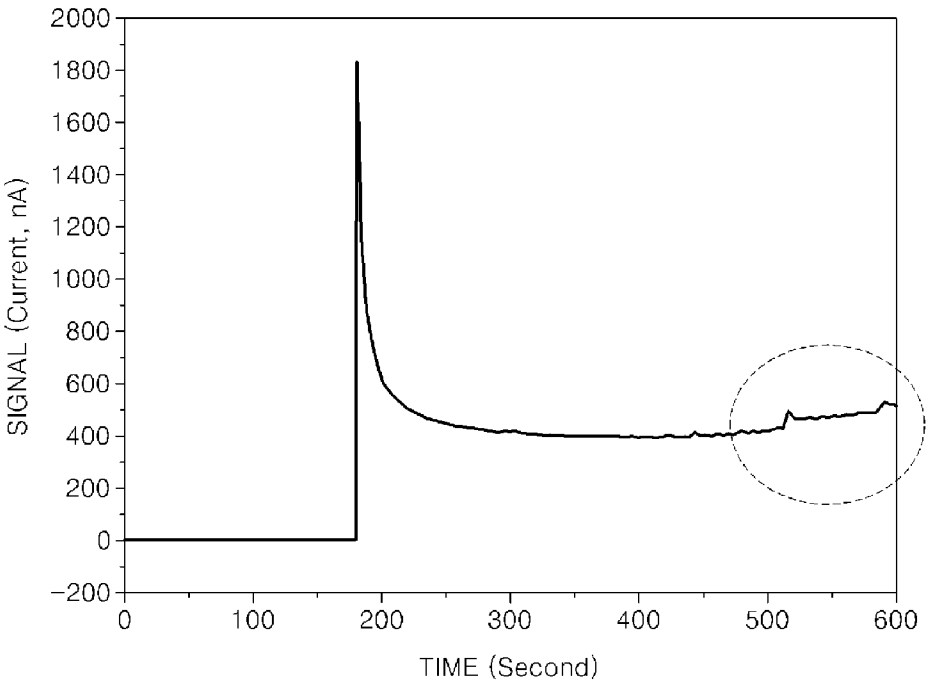


FIG. 3A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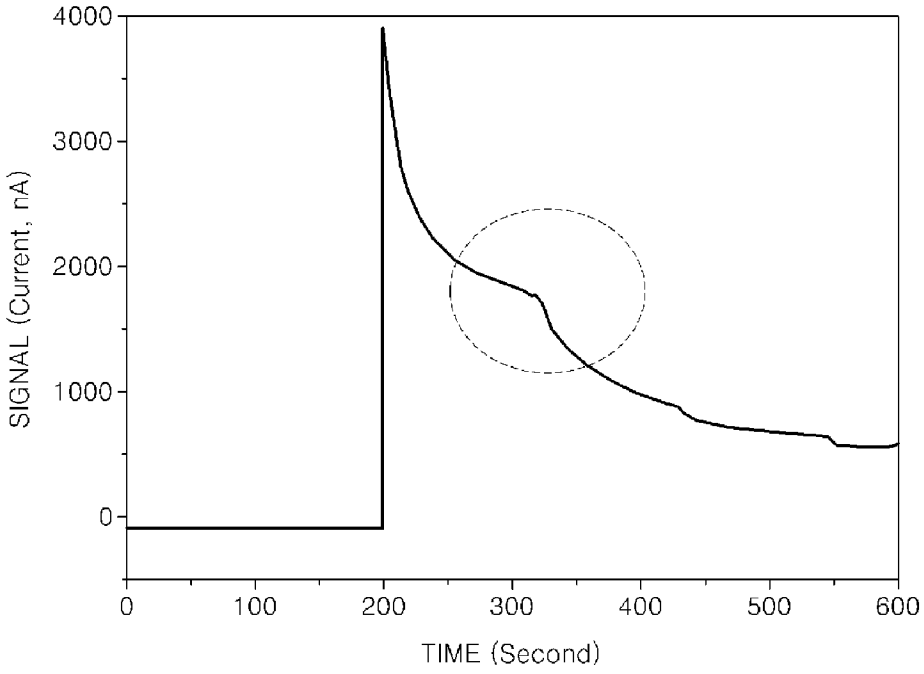
TIME (Second)

FIG. 3B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TIME (Second)

FIG. 4

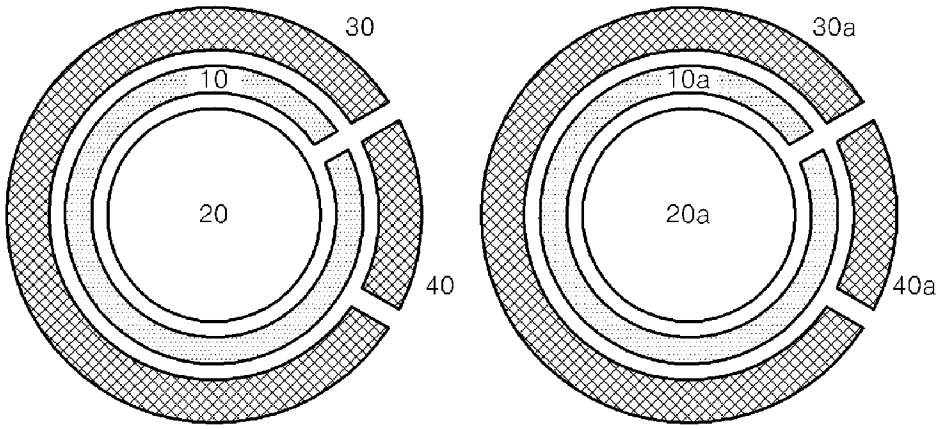
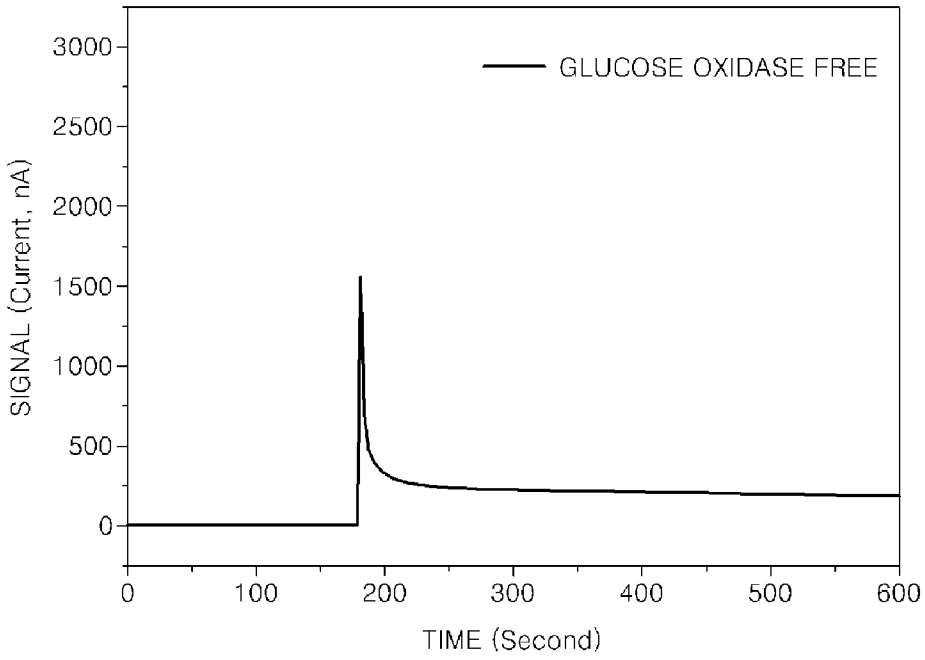


FIG. 5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TIME (Second)

FIG. 6

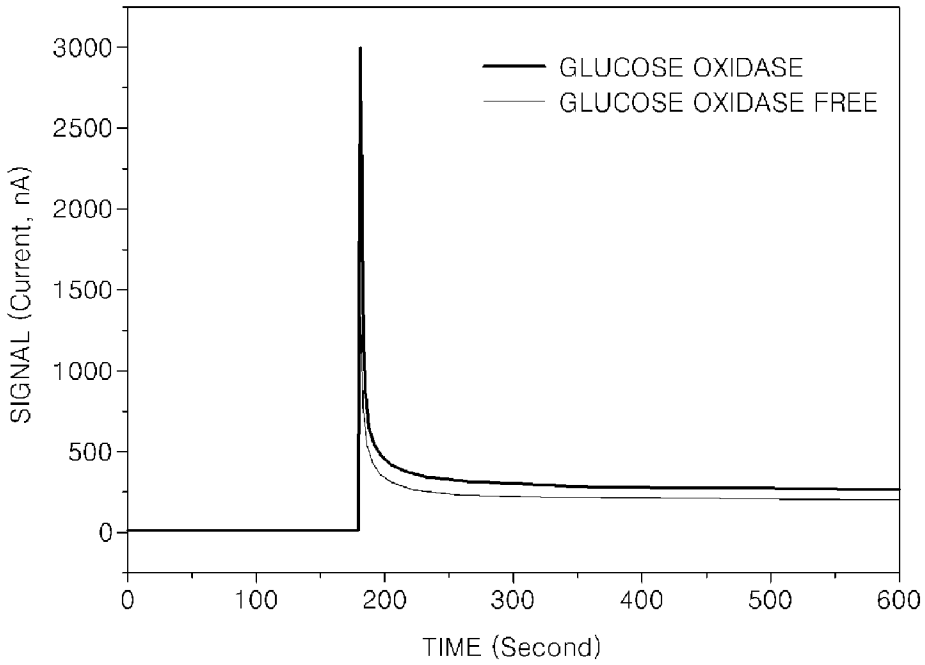
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FIG. 7A

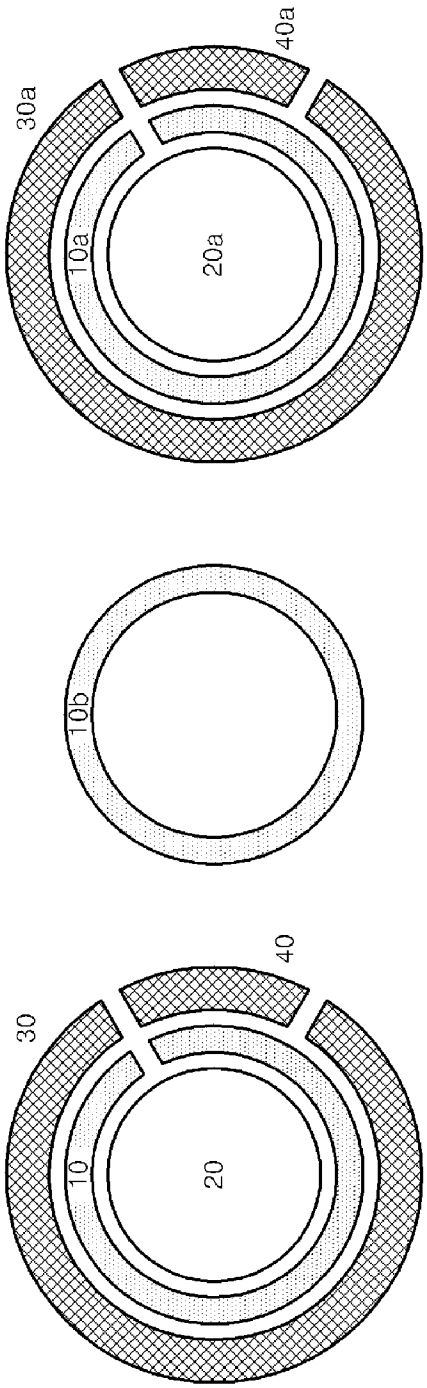


FIG. 7B

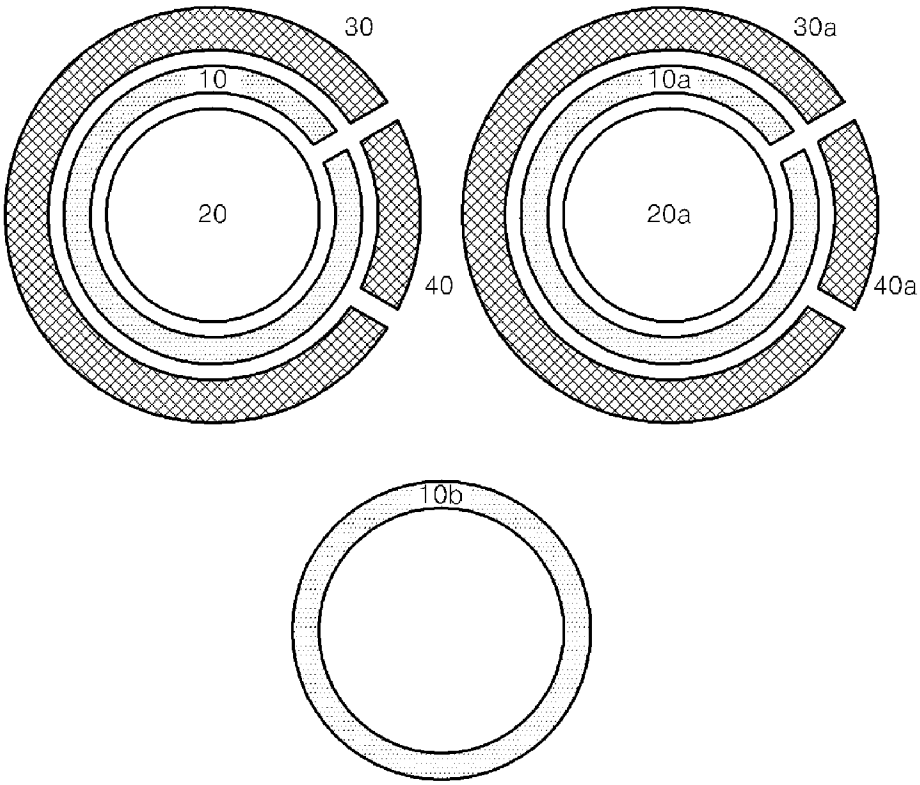
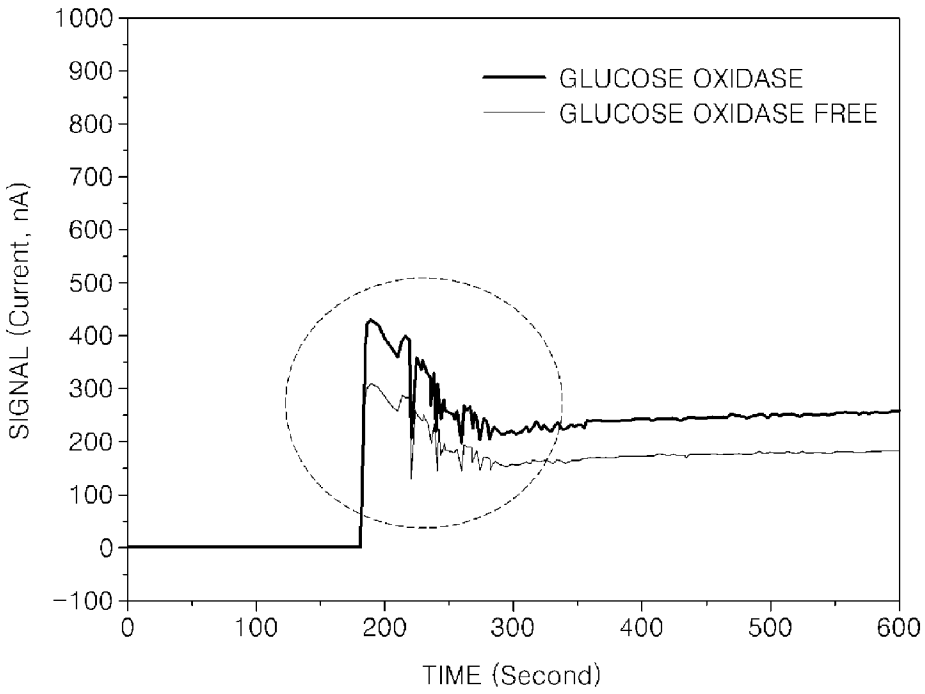


FIG. 8A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TIME (Second)
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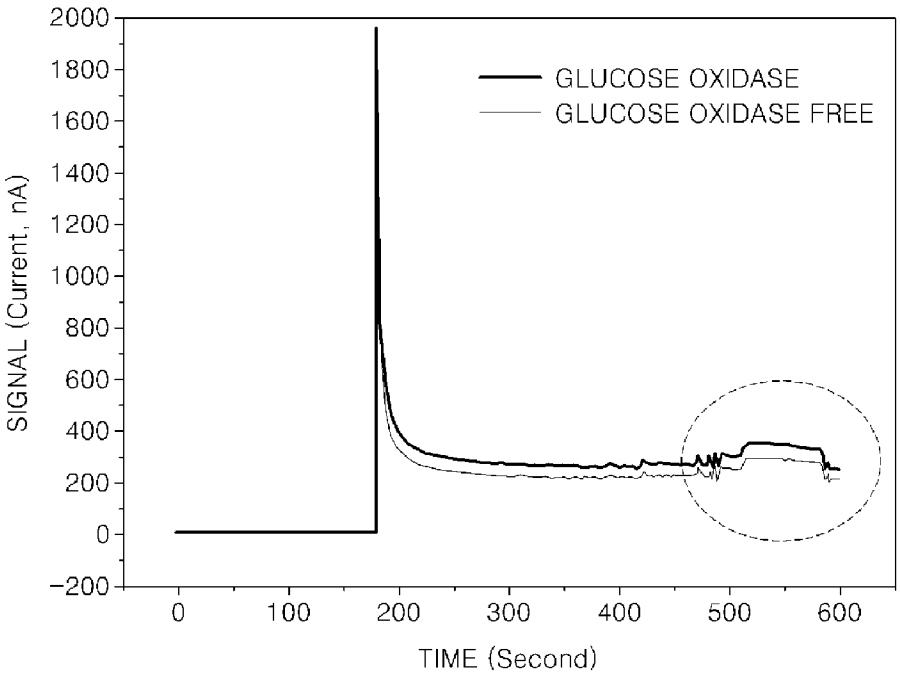
FIG. 8B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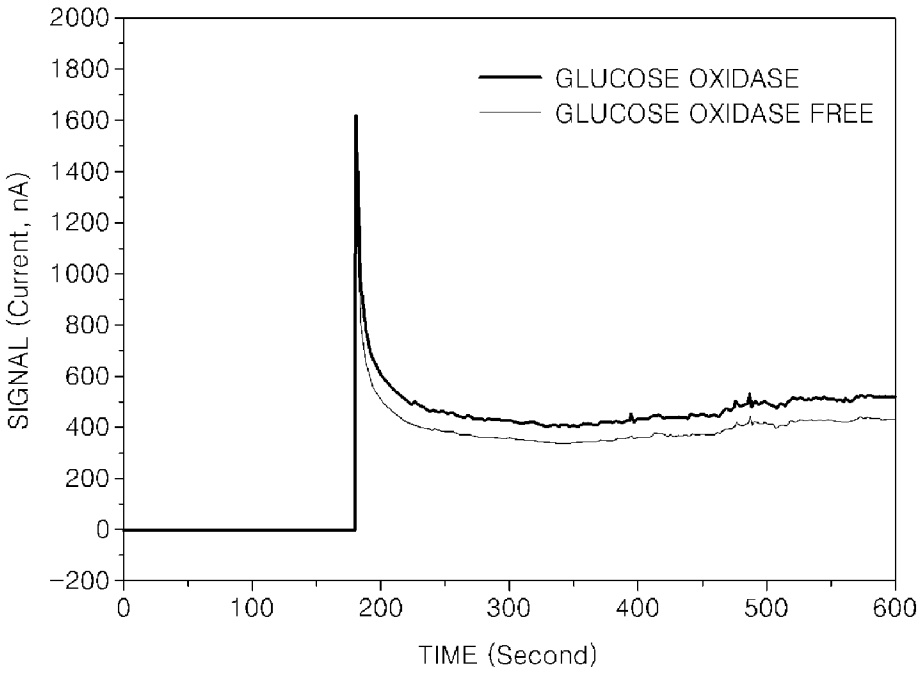
TIME (Second)
GLUCOSE OXIDASE
GLUCOSE OXIDASE FREE

FIG. 8C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GLUCOSE OXIDASE FREE
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TIME (Second)
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2008/001793

A. CLASSIFICATION OF SUBJECT MATTER

A61B 5/1486(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 8 G01N 33/48 , G01N 33/49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean Utility models and applications for Utility models since 1975

Japanese Utility models and applications for Utility models since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKIPASS (KIPO internal)&Keyword : "stem, (wand, stick, straw), extract, sponge, wall, vial, "

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KR 20-0433455 Y1(KMH CO. LTD) 8 December 2006	1
A	See abstract; claims1-9 ; figures 1-3	2~10
Y	US 6,587,705 B1(LYNN KIM, et al.) 1 Jury 2003	1
A	See abstract; claims1,20,47 ; figures 2-3	2~10

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

☒ See patent family annex.

* Special categories of cited documents:

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 JULY 2008 (09.07.2008)	**09 JULY 2008 (09.07.2008)**

Name and mailing address of the ISA/KR

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Facsimile No. 82-42-472-7140

Authorized officer

PARK Mi Jeong

Telephone No. 82-42-481-8379

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2008/001793

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		US 6999810 BB	14.02.2006