CONTINUOUS PROCESS FOR MANUFACTURE OF DISPOSABLE ELECTRO-CHEMICAL SENSOR

DESCRIPTION

BACKGROUND OF THE INVENTION

This application relates to electrochemical sensors useful for detection and/or quantification of a target analyte in a sample.

Disposable electrochemical sensors for monitoring of target analytes in blood or urine are well known. In particular, electrochemical measurement of the amount of glucose in a small amount of blood using disposable electrochemical sensors and small, portable meters has become a mainstay of many diabetics. These home-use systems permit routine measurements and provide the diabetic with an increased ability to self-manage his or her condition.

The disposable electrochemical sensors used in these devices are generally formed as a series of patterned layers supported on a substrate. Mass production of these devices has been carried out by screen printing and other deposition processes, with the multiple layers making up the device being deposited *seriatim* in a batch process.

Manufacture of disposable electrochemical sensors by these techniques has several drawbacks. First, operation in batch mode is fundamentally inefficient. Multiple steps in the process requires the use of multiple print lines, one for each layer in the device. Not only does this increase the capital expense for the manufacturing equipment it also introduces multiple opportunities for process variation such as variable delays and storage conditions between print steps, as well as variations in the process itself such as registration drift between different process stations. Such process variations can result in poor calibration of some sensor batches resulting in potentially erroneous reading when the electrodes are used.

A potential second drawback arises from a characteristic inherent to screen printing, namely the thickness of the deposited layers. Standard screen printing processes can be used to deposit layers from 1 to 100 μm in thickness. Heat-cured resins can be used to obtain thinner layers of less than 1 μm in thickness. For printing

electrodes, the capability of screen printing to produce layers with these dimensions is beneficial, since the thicker print has greater conductivity. For reagent layers, for example layers of enzymes which are utilized in many disposable electrochemical reactions, however, thick layers are detrimental to the reliable operation of the device. Specifically, because the amount of signal generated by a device of this type depends on the inter-reaction of these reagents and the target analyte within a very narrow region at the electrode surface, the use of reagent layers which extend beyond this region reduces the measured signal by depleting inwardly migrating analyte before it can reach the measurement zone.

In view of these drawbacks, there is a need for a new approach to the manufacture of disposable electrochemical sensors. It is an object of the present invention to meet this need.

It is a further object of this invention to provide a method for manufacturing disposable electrochemical sensors which operates as a continuous process and which provides for deposition of thin reagent layers.

It is a further object of the invention to provide cassettes which incorporate spooled sensors, including spooled sensors manufactured using the method of the invention.

It is a further object of the invention to provide sensors which having an integrated sealing layer which is combination with the substrate produce a sealed sample receiving chamber, thereby protecting the reagents until time of use, which sensors can be made using the method of the invention.

SUMMARY OF THE INVENTION

These and other objects of the invention are met by a method in accordance with the invention for manufacturing electrochemical sensors. The sensors comprises a substrate, an electrode layer and at least a first reagent layer. The method comprises the steps of transporting a continuous web of the substrate past at least two print stations, and printing the electrode layer and the first reagent layer on the substrate. One of the print stations prints the electrode layer on the continuous web of substrate, and the other of the print stations prints the first reagent layer on the continuous web

of substrate as it is transported past the print stations. Additional print stations may be included for the printing of insulation layers, glue prints and the like. The order of printing will depend on the structure desired for the sensor, although the electrode layer(s) will frequently be deposited before the reagent layer(s).

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1A and 1B show two alternative deposition patterns useful in the method of the invention;

Figs. 2A and 2B show an exemplary electrochemical sensor which can be manufactured using the method of the invention;

Fig. 3 shows a schematic view of an apparatus for practicing the method of the invention;

Fig. 4 shows post-processing of a web printed with sensors to produce sensor spools;

Figs 5A and 5B shows cassettes useful with the sensor spool of Fig. 4, Fig. 5C shows a meter in combination with the cassette of Fig. 5A;

Fig. 6 shows an alternative embodiment of a sensor which can be manufactured using the method of the invention;

Figs. 7A and B shows a further alternative embodiment of a sensor which can be manufactured using the method of the invention; and

Figs. 8 A, B and C shows the application of a sealing layer to a ribbon of test strips in accordance with the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for manufacturing electrochemical sensors using a continuous web of substrate transported past a plurality of printing stations for deposition of various layers making up the sensor. The method can be used for making sensors which are directed to any electrochemically-detectable analyte.

Exemplary analytes of particular commercial significance for which sensors can be made using the method include; glucose, fructosamine, HbAIC, lactate, cholesterol, alcohol and ketones.

The specific structure of the electrochemical sensor will depend on the nature of the analyte. In general, however, each device will include an electrode layer and at least one reagent layer deposited on a substrate. As used in the specification and claims hereof, the term "layer" refers to a coating applied to all or part of the surface of the substrate. A layer is considered to be "applied to" or "printed on" the surface of the substrate when it is applied directly to the substrate or the surface of a layer or layers previously applied to the substrate. Thus, deposition of two layers on the substrate may result in a three layer sandwich (substrate, layer 1, and layer 2) as shown in Fig. 1A or in the deposition of two parallel tracks as shown in Fig. 1B, as well as intermediate configurations with partial overlap.

In the method of the invention, the electrochemical sensors are printed in a linear array, or as a plurality of parallel linear arrays onto a flexible web substrate. As discussed below, this web may be processed by cutting it into ribbons after the formation . As used in the specification and claims of this application, the term "ribbon" refers to a portion of the printed web which has been formed by cutting the web in either or both of the longitudinal and tranverse directions, and which has a plurality of electrochemical sensors printed thereon.

Figs. 2A and 2B show the structure of an electrochemical sensors for detection of glucose in accordance with in the invention. On the substrate 10 are placed a conductive base layer 16, a working electrode track 15, a reference electrode track 14, and conductive contacts 11, 12, and 13. An insulating mask 18 is then formed, leaving a portion of the conductive base layer 16, and the contacts 11, 12 and 13 exposed. A reagent layer of a working coating 17, for example a mixture of glucose oxidase and a redox mediator, is then applied over the insulating mask 18 to make contact with conductive base layer 16. Additional reagent layers can be applied over working coating 18 if desired. For example, the enzyme and the redox mediator can be applied in separate layers.

It will be appreciated that the specific structure shown in Figs. 2A and 2B is merely exemplary and that the method of the invention can be used to manufacture electrochemical sensors for a wide variety of analytes and using a wide variety of electrode/reagent configurations. Exemplary sensors which could be manufactured using the method of the invention include those disclosed in European Patent No. 0 127 958, and US Patents Nos. 5,141,868, 5,286,362, 5,288,636, and 5,437,999, which are incorporated herein by reference.

Fig. 3 shows a schematic view of an apparatus for practicing the invention. A running web of substrate 31 is provided on a feed roll 32 and is transported over a plurality of print stations 33, 34, and 35, each of which prints a different layer onto the substrate. The number of print stations can be any number and will depend on the number of layers required for the particular device being manufactured. Between successive print stations, the web is preferably transported through a dryer 36, 37, and 38 (for example a forced hot air or infra-red dryer), to dry each layer before proceeding to the deposition of the next. After, the final dryer 38, the printed web is collected on a take up roll or introduced directly into a post-processing apparatus 39.

While the most efficient embodiments of the invention will generally use a plurality of print stations as illustrated in Fig. 3 for the printing of different materials, it will be appreciated that many of the advantages of the invention can be achieved with a process in which a single print station is used several times with different print reagents. In particular, benefits of increased throughput and improved print registration are obtained when using the same print station multiple times. Thus, as used in the specification and claims of this application, the phrase "at least two print stations" refers both to embodiments in which two or more distinct print stations are employed and to embodiments in which a common print station is used in several passes to print the required materials onto the substrate.

As noted above, one of the most important parameters to control when printing the various layers of a bionsesor is the thickness of the deposited layer, particularly with respect to the reagent layer. The thickness of the printed layer is influenced by various factors, including the angle at which the substrate and the screen are separated. In a conventional card printing process, where the substrate is presented as

individual cards on a flat table, this angle varies as the squeegee moves across the screen, leading to variations in thickness and therefore to variations in the sensor response across the card. To minimize this source of variation, the print stations used in the method of the present invention preferably makes use of cylinder screen printing or rotogravure printing.

In cylinder screen printing, a flexible substrate is presented to the underside of a screen bearing the desired image using a cylindrical roller and moves synchronously with the squeegee. Unlike conventional printing, where the screen moves away from a stationary substrate, in this process the moving substrate is pulled away from the screen. This allows a constant separation angle to be maintained, so that a uniform thickness of deposit is achieved. What is more, the contact angle, and thus the print thickness can be optimized by choosing the appropriate point of contact. By appropriate optimization, the process can be engineered so that the ink is pulled out of the screen and transferred to the substrate much more efficiently. This sharper "peel off" leads to much improved print accuracy, allowing a finer detail print. Therefore smaller electrodes can be printed and smaller overall sensors can be achieved.

The post-processing apparatus 39 may perform any of a variety of treatments, or combinations of treatments on the printed web. For example, the post processing apparatus may apply a cover over the electrochemical devices by laminating a second continuous web to the printed substrate. The post-processing apparatus may also cut the printed web into smaller segments. To produce individual electrochemical devices of the type generally employed in known hand-held glucose meters, this cutting process would generally involve cutting the web in two directions, longitudinally and laterally. The use of continuous web technology offers the opportunity to make electrochemical sensors with different configurations which offer advantages for packaging and use.

As shown in Fig. 4, the printed web can be cut into a plurality of longitudinal ribbons, each one sensor wide. These ribbons can in turn be cut into shorter ribbons of convenient lengths, for example, 10, 25, 50 or even 100 sensors. These ribbons may be rolled into spools and packaged into a cassette which is inserted into a meter

(Fig. 5A). Alternatively, a short ribbon of say 5 strips can be prepared to provide enough sensors for one normal day of testing. For this length, a cassette is probably not necessary, although it could be provided if desired. In either case, the sensors are used one and a time, and moved into the appropriate position at the time of use. Preferably, this movement is accomplished by a meter-resident mechanism, which also prevents used strips from being drawn back inside the meter.

The use of spooled ribbons with multiple sensors has substantial advantages over the known systems using single electrochemical sensors. Because the spooled electrochemical devices are packaged inside a cassette, they are less susceptible to damage. Further, since the spool of devices is a continuous strip and is not intended to be removed from the cassette prior to use, there is less likelihood that a sensor will be used with the wrong calibration codes. The risk of erroneous calibration values can be further reduced if the cassette and the meter interact to provide calibration values for the sensors contained within the cassette. Interactions of this type are described for individual sensor devices in International Patent Publication No. WO97/29847 and US Patent Application No. 08/600,449 which are used herein by reference.

A further advantage of continuous spools of electrochemical sensors is the ability to make each individual smaller. Much of the size of known individual sensors is driven by a requirement that the user be able to manipulate the sensor for insertion in the meter. Use of a continuous spool of sensors eliminates these constraints on the size of the device since the user will be manipulating the cassette or ribbon of electrochemical sensors which will be significantly easier to handle than individual strips. Thus, the present invention permits the fabrication of smaller and therefore more economical devices.

If it is desired to separate used devices from the spool, a cutter may be incorporated into the meter or into the cassette. A cutter of this type is disclosed in US Patent No. 5,525,297, which is incorporated herein by reference, although other configurations could be employed.

Fig. 5B shows variation of the meter of Fig. 5A. In this case, the cassette includes a take up mechanism such that the sensor spool is transferred from a feed

spool 51 to a take up spool 52 as it is used. This makes the entire cassette system self-contained and eliminates the need to dispose of individual sensors which have frequently been contaminated with blood.

The method of the invention can also be used to produce sensor spools having parallel arrays of sensors of different types. Thus, as shown in Fig. 6, a sensor strip could be prepared in which sensors of a first type, 61 are disposed alongside sensors of a second type, 62. By providing separate contacts and analysis circuitry for each sensor, two values can be determined simultaneously in the same meter with the same sample. Suitable analyte pairs include glucose and glycosylated hemoglobin; and LDL and HDL. Two different sensors measuring levels of the same analyte might also be employed to provide and internal check, or to increase the dynamic range of the strip.

The method of the invention also facilitates the manufacture of sensors having structures which cannot be conveniently produced using conventional batch processing. For example, as shown in Figs. 7A and 7B, a device can be manufactured by depositing parallel conductive tracks 71 and 72; reagent layer(s) 73 and an insulation layer 74 on a substrate 70. The substrate is then folded along a fold line disposed between the two conductive tracks to produce a sensor in which two co-facial electrodes are separated by a reagent layer. An electrode geometry of this type is beneficial because the voltage drop due to solution resistance is low as a result of the thin layer of solution separating the electrodes. In contrast, in a conventional device with coplanar electrodes, the use of a thin layer of solution results in a substantial voltage drop along the length of the cell and concomitant uneven current distribution. Furthermore the device of Figs. 7A and 7B can be cut across the deposited reagent to produce a very low volume chamber for sample analysis which further improves the performance of the device.

As is apparent from the foregoing discussion, the method of the present invention provides a very versatile approach for manufacture of electrochemical sensors. The following discussion of suitable materials which can be used in the method of the invention is intended to further exemplify this versatility and not to limit the scope of the invention which is defined by the claims.

The substrate used in the method of the invention may be any dimensionally stable material of sufficient flexibility to permit its transport through an apparatus of the type shown generally in Fig. 3. In general the substrate will be an electrical insulator, although this is not necessary if a layer of insulation is deposited between the substrate and the electrodes. The substrate should also be chemically compatible with the materials which will be used in the printing of any given sensor. This means that the substrate should not significantly react with or be degraded by these materials, although a reasonably stable print image does need to be formed. Specific examples of suitable materials include polycarbonate and polyester.

The electrodes may be formed of any conductive material which can be deposited in patterns in a continuous printing process. This would include carbon electrodes and electrodes formed from platinized carbon, gold, silver, and mixtures of silver and silver chloride.

Insulation layers are deposited as appropriate to define the sample analysis volume and to avoid a short circuiting of the sensor. Insulating materials which can be printed are suitable, including for example polyester-based inks.

The selection of the constituents of the reagent layer(s) will depend on the target analyte. For detection of glucose, the reagent layer(s) will suitably include an enzyme capable of oxidizing glucose, and a mediator compound which transfers electrons from the enzyme to the electrode resulting in a measurable current when glucose is present. Representative mediator compounds include ferricyanide, metallocene compounds such as ferrocene, quinones, phenazinium salts, redox indicator DCPIP, and imidazole-substituted osmium compounds. The reagents appropriate to other types of sensors will be apparent to persons skilled in the art.

One of the limitations of any device in which multiple test elements are stored within a test device is that the elements must be made stable for the expected lifetime of the test elements within the test device. In general, for electrochemical sensor strips, this means providing a moisture-proof and air-tight environment for unused sensor strips. This can be accomplished through the design of the cassette and associated meter, or it may be accomplished by adding a sealing layer to the test

ribbon so that individual test strips are individually sealed and protected from moisture.

Figs. 8 A-C relate to ribbons of test strips with a sealing layer. Fig. 8A shows a composite structure comprising a lower layer ribbon of test strips 80 and an upper sealing layer 81. The upper sealing layer 81 is shown partially peeled back to expose the first test element. The upper layer contains apertures 82 through which electrical contact with the underlying test strip can be made. The sealing layer 81 is typically attached to the ribbon 80 using a hot melt or pressure-sensitive adhesive. The meter employed with the sealed test strip ribbon of Fig. 8A would include a mechanism, such as a knife blade, for peeling back the sealing layer 81 to expose the target area of a strip that is about to be used. After use, the used test strip and the peeled back sealing layer may be cut away from the unused portion of the ribbon, for example using a cutter blade integral to the cassette. The used strips and peeled of sealing layer might also be rolled up onto take-up spools within a cassette as shown in Fig. 8B, thus avoiding the need for a user to contact used strips directly.

Fig. 8C shows a variation on the structure of Fig. 8C. In this case, the sealant layer serves as one wall of the test strip sample chamber. This geometry has certain advantages, notably that evaporative cooling of the sample (which can lead to erroneously low readings) is reduced. To prepare a test strip on a ribbon of this type for use, a cut is made which opens the end of a chamber formed by the sealing layer 81 and the test strip ribbon 80. In Fig. 8C, separate cut line-types 88 and 89 are shown for separating used devices and for opening a new device, respectively. These cuts can be made at the same type or at different times.

CLAIMS

1. A method for manufacturing electrochemical sensors comprising a substrate, an electrode layer comprising a plurality of electrode pairs and at least a first reagent layer, said method comprising the steps of transporting a continuous web of the substrate past at least two print stations and printing the electrode layer, said electrode layer and the first reagent layer on the substrate, one of said print stations printing the electrode layer on the continuous web of substrate and the other said print stations printing the first reagent layer on the continuous web of substrate as it is transported past the print stations.

2. The method of claim 1, wherein the plurality of electrode pairs comprises a first and second electrode each having a different measuring capability.

3. The method of claim 1 or 2, wherein the electrochemical sensors further comprise a second reagent layer which is deposited on the continuous web substrate by a third print station.

4. A method for manufacturing electrochemical sensors comprising a substrate, an electrode layer, a first reagent layer and a second reagent layer, said method comprising the steps of transporting a continuous web of the substrate past at least three print stations and printing the electrode layer, the first reagent layer and the second reagent layer on the substrate, the first of said print stations printing the electrode layer on the continuous web of substrate, the second print station printing the first reagent layer on the continuous web of substrate and third print station printing the second reagent layer on the continuous web substrate as it is transported past the print stations.

5. The method of any one of claims 1 to 4, wherein the print stations are rotogravure print stations.

6. The method of any one of claims 1 to 4, wherein the print stations are cylinder screen printing stations.

7. The method of any of one of claims 1 to 6, wherein the electrochemical sensors detect glucose.

8. The method of claim 7, wherein the first reagent layer comprises glucose oxidase.

9. The method of any one of claims 3 to 8, wherein the second reagent layer comprises an electron transfer mediator.

10. The method of claim 9, wherein the electron transfer mediator is ferricyanide.

11. The method of any of the preceding claims, wherein the print stations which print the electrode layer and the first reagent layer are separate and distinct print stations.

12. The method of any one of claims 3 to 10, wherein the print stations which print the electrode layer, the first reagent layer and the second reagent layer are separate and distinct print stations.

13. The method of claim 11 or 12, wherein the continuous web of substrate is transported between the print stations in a continuous process.

14. The method of any one of claims 11 to 13, wherein the continuous web of substrate is transported through a dryer between the print stations.

15. The method of claim 15, wherein the dryer is an infra-red dryer.

16. The method of any one of the preceding claims, further comprising a sealing post processing step applied to the web after printing of the electrochemical sensors in which a sealing layer is applied over the electrochemical sensors.

17. The method of claim 16, wherein the sealing layer and the web having the electrochemical sensors printed thereon cooperate to form a sample-receiving chamber which can be opened by cutting the end of a sensor.

18. The method of any of the preceding claims, further comprising a cutting post processing step applied to the web after printing of the electrochemical sensors in which the web is cut into ribbons, each ribbon containing a plurality of sensors.

19. The method of claim 18, wherein each ribbon contains from 5 to 100 sensors.

20. A cassette comprising a case and a ribbon disposed within the case on which a plurality of disposable electrochemical sensors, printed in a coplanar manner with said ribbon, are provided.

21. The cassette according to claim 20, wherein the electrochemical sensors are for the detection of glucose.

22. The cassette of claim 20, wherein the sensors are manufactured in accordance with the method of any one of claims 1 to 19.

23. An electrochemical sensor for the detection of an analyte such as glucose, wherein the sensor is printed on a substrate and is covered by a sealing layer, said substrate and sealing layer cooperating to form a sealed sample-receiving chamber, and wherein in use the sealed sample-receiving chamber is cut to produce an opening to the sample-receiving chamber for the introduction of analyte to the sample.

24. A continuous web of electrochemical sensors, said electrochemical sensors being adapted for the detection for glucose in blood said continuous web comprising:

a plurality of electrode pairs comprising first and second electrodes screen printed in a linear array on a continuous sheet of flexible substrate material;

a reagent layer screen printed over said web such that said reagent covers at least one of said first and second electrodes of each of said pair of electrodes;

a sealing layer positioned over said regent layer and said electrodes to form a sample receiving area chamber.

25. The sensor of claim 24, wherein the first and second electrode each have a different measuring capability

26. The sensor according to claim 24 or 25, wherein said reagent layer comprises glucose oxidase.

27. The sensor according to claim 26, further comprising an electron transfer mediator.

28. The sensor according to claim 27, wherein the electron transfer mediator is selected from the group consisting of ferricyanide, metallocene compounds, quinines, phenazinium salts, redox indicator DCPIP, and imidiazole substituted osmium compounds.

29. The sensor according to claim 28, wherein the sensor comprises electrodes selected from the group consisting of carbon electrodes and electrodes formed from platinized carbon, gold, silver, and mixtures of silver and silver chloride.