ANALYTE SENSOR AND METHOD FOR MANUFACTURING AN ANALYTE SENSOR

Description

CLAIM OF PRIORITY

[001] This application claims the benefit of U.S. Provisional Patent Application No. 63/218510, which is entitled "ANALYTE SENSOR AND METHOD FOR MANUFACTURING AN ANALYTE SENSOR," and was filed on July 6, 2021 and claims the benefit of EP Application No. 21183849.5, which is entitled "ANALYTE SENSOR AND METHOD FOR MANUFACTURING AN ANALYTE SENSOR," and was filed on July 6, 2021, and the entire contents of each application are incorporated herein by reference.

FIELD

[002] The present disclosure relates to an analyte sensor comprising a substrate, at least one working electrode, at least one second electrode and a membrane, wherein the membrane is located on top of the at least one second electrode. The present disclosure further relates to a process for manufacturing the ~~inventive~~ analyte sensor as well as to an analyte sensor system comprising an analyte sensor according to the present disclosure and an electronics unit. The analyte sensor according to the present disclosure may mainly be used for conducting an analyte measurement in a body fluid of a user.

BACKGROUND

[003] Biosensors for measuring analytes in biological fluids, in particular a sensor which is designed for implantation or subcutaneous insertion to measure body fluids, have to fulfill a variety of functions: on the one hand, the sensor must provide for specific and sensitive measurement without interference from e.g. particular components of body fluids. For this purpose, biosensors are frequently covered with membranes excluding particular compounds in order to allow access to the actual sensing sites only for low molecular weight compounds. While the specificity of biosensors is achieved by using biorecognition elements, such as enzymes, the sensitivity is often tailored by using diffusion limiting membranes. Finally, the implanted sensor must be biocompatible, where the inflammation reaction in the body is minimized, and for this purpose, an additional biocompatibility membrane may be applied.

[0013] It is therefore desirable to provide an analyte sensor which avoids at least in part certain drawbacks of the prior art, in particular with regard to its manufacturability and also with regard to its long-term stability and good performance in use.

SUMMARY

[0014] This section provides a general summary of the disclosure, and is not a comprehensive disclosure of its full scope or all of its features. Further areas of applicability and aspects of the invention will become apparent from the claims, the figures and the description provided herein. The description in this summary is intended for purposes of illustration only and is not intended to limit the scope of the present disclosure.

[0015] At least one of the above-described issues/problems is solved by an analyte sensor according to independent claim 1 as well as by the method for manufacturing a sensor according to independent claim 12 and by the analyte sensor system according to independent claim 18. Preferred embodiments of the invention which may be realized in an isolated way or in any arbitrary combination are disclosed in the dependent claims and throughout the specification and the figures.

[0016] The ~~inventive~~ analyte sensor is particularly easy to manufacture. It furthermore exhibits an excellent long-term stability and a stable sensitivity. In particular, the ~~inventive~~ analyte sensor allows the analyte sensor to comprise only two electrodes instead of three, which makes the ~~inventive~~ analyte sensor particularly cost-efficient. Further, it has an improved biocompatibility.

[0017] As used in the following, the terms “have”, “comprise”, or “include” or any arbitrary grammatical variations thereof are used in an exclusive way. Thus, these terms may both refer to a situation in which,

[0018] besides the feature introduced by these terms, no further features are present in the entity described in this context and to a situation in which one or more further features are present. As an example, the expressions “A has B”, “A comprises B” and “A includes B” may both refer to a situation in which, besides B, no other element is present in A (i. e. a situation in which A solely and exclusively consists of B) and to a situation in which, besides B, one or more further elements are present in entity A, such as element C, elements C and D or even further elements.

[0019] Further, it should be noted that the terms "at least one", "one or more" or similar expressions indicating that a feature or element may be present once or more than once typically will be used only once when introducing the respective feature or element. In the following, in most cases, when referring to the respective feature or element, the expressions "at least one" or "one or more" will not be repeated, notwithstanding the fact that the respective feature or element may be present once or more than once.

[0020] Further, as used in the following, the terms "preferably", "more preferably", "particularly", "more particularly", "specifically", "more specifically" or similar terms are used in conjunction with optional features, without restricting alternative possibilities. Thus, features introduced by these terms are optional features and are not intended to restrict the scope of the claims in any way. The invention may, as the skilled person will recognize, be performed by using alternative features. Similarly, features introduced by "in an embodiment of the invention" or similar expressions are intended to be optional features, without any restrictions regarding alternative embodiments of the invention, without any restrictions regarding the scope of the invention and without any restrictions regarding the possibility of combining the features introduced in such way with the optional or nonfunctional features of the invention.

[0021] A first aspect of the present invention relates to an analyte sensor which comprises

- a substrate comprising a first side and a second side;
- at least one working electrode positioned on the first side of the substrate, the at least one working electrode comprising:
  - at least one electrically conductive material and
  - at least one enzyme;
- at least one second electrode positioned on the second side of the substrate, the at least one second electrode comprising at least one first silver layer and at least one second silver layer, wherein the second silver layer at least partially overlaps with the first silver layer, wherein the first and second silver layers comprise different compositions, wherein the first and the second silver layers comprise AgCl and wherein the first silver layer includes a lower weight % of AgCl than the weight % of AgCl of the second silver layer based on the total weight of the first silver layer and the total weight of the second silver layer; and
- a membrane comprising a polymer composition which comprises a hydrophobic polymer, wherein the membrane is located on top of the at least one second electrode,
- wherein the sensor comprises at least one exposed area of the first silver layer, said at least one exposed area being disposed on the exterior of the sensor and configured to be in direct contact with body fluid when the sensor is implanted in a user.

[0022] In another aspect of the present invention, a method is provided for manufacturing an analyte sensor~~, in particular the inventive analyte sensor~~, the method comprising the steps:

a) providing a raw substrate which comprises a first side and a second side;

b) preparing a working electrode region on the first side of the raw substrate, the preparing of the working electrode region comprising the steps:

b1) applying an electrically conductive material to the first side of the raw substrate,

b2) applying a sensing material comprising at least one enzyme at least partially on the electrically conductive material;

c) preparing a second electrode region on the second side of the raw substrate, the preparing of the second electrode region comprising the steps:

c1) applying a first silver composition to form a first silver composition region on the second side of the raw substrate,

c2) applying a second silver composition as a plurality of separated regions over the first silver composition region such that the second silver composition regions ~~at least~~ partially overlap with the first silver composition region, wherein the second silver composition has a different composition than the first silver composition, wherein the first silver composition and the second silver composition each comprise AgCl and the first silver composition includes a lower weight % of AgCl than the second silver composition based on the total weight of the first silver composition and the total weight of the second silver composition;

d) applying a polymer composition on top of the second electrode region, to obtain a membrane, wherein the polymer composition comprises a hydrophobic polymer; and

e) cutting the raw substrate, the working electrode region, the second electrode region and the membrane, wherein only the first silver composition region of the second electrode region is cut such that the first silver composition region comprises at least one exposed area configured to be in direct contact with body fluid when the sensor is implanted in a user.

[0023] The term "analyte sensor" within the context of the present invention may refer to any device being configured for the detection of an analyte.

[0024] The term "analyte" may refer to any arbitrary element, component or compound which may be present in a body fluid and the concentration of which may be of interest for the user. Preferably, the analyte may be or may comprise an arbitrary chemical substance or chemical compound which may take part in the metabolism of the user, such as at least one metabolite. As an example, the analyte may be selected from the group consisting of glucose, cholesterol, triglycerides, and lactate. Additionally or alternatively, however, other types of analytes and/or any combination of analytes may be determined. Preferably, the analyte is glucose.

analyte sensor may be configured for detecting the analyte within the body tissue. The analyte sensor is in one embodiment suitable for short-term application, e. g. 3 to 21 days, preferably 7 to 21 days, preferably 14 to 21 days, or for long-term application e. g. 1 to 12 months. During its application, the analyte may be determined by continuous or discontinuous measurements.

[0029] The analyte sensor of the invention is an electrochemical sensor comprising at least one working electrode and at least one second electrode. More particularly, the sensor is an amperometric electrochemical sensor comprising the at least one working electrode and the at least one second electrode. The working electrode is sensitive for the analyte to be measured at a polarization voltage which may be applied between the at least one working electrode and the at least one second electrode and which may be regulated by a potentiostat. A measurement signal may be provided as an electric current between the at least one working electrode and the at least one second electrode.

[0030] The ~~inventive~~ analyte sensor comprises a substrate which comprises a first side and a second side.

[0031] Within the context of the present invention, the term "substrate" specifically may refer, without limitation, to any kind of material or combination of materials which is suitable to form a carrier layer to support the at least one working electrode and the at least one second electrode. In particular the substrate may comprise an electrically insulating material. Within the context of the present invention "electrically insulating material" is a broad term and given its ordinary and customary meaning to a person of ordinary skill in the art. The term "electrically insulating material" may also encompass a dielectric material. The term specifically may refer, without limitation, to a material or combination of materials which prevent the transfer of electrical charges and which do not sustain a significant electrical current. Specifically, without limiting other possibilities, the at least one electrically insulating material may be or may comprise at least one insulating resin such as insulating epoxy resins used in manufacturing of electronic printed circuit boards. In particular, it may comprise or be at least one thermoplastic material such as a polycarbonate, a polyester, a polyvinylchloride, a polyurethane, a polyethylene, a polypropylene, polystyrene, a polyether, a polyamide, a polyimide, polytetrafluoroethylene or a copolymer thereof. In an embodiment, the at least one electrically insulating material may comprise or may be alumina. Suitable polyesters are, for example, selected from the group consisting of polyethylene terephthalate (PET), glycol modified polyethylene

hydrogels such as hydrogels prepared from the copolymerization of 2-hydroxyethyl methacrylate (HEMA), 2-hydroxypropyl methacrylate (HPMA), acrylamide (AAm), acrylic acid (AAc), N-isopropylacrylamide (NIPAm), and methoxyl poly(ethylene glycol) (PEG) monoacrylate (mPEGMA or PEGMA), with cross-linkers, such as N,N′-methylenebis(acrylamide) (MBA), ethylene glycol diacrylate (EGDA) and PEG diacrylate (PEGDA), Pluronic® polymers with a structure of poly(ethylene oxide) (PEO)-poly(propylene oxide) (PPO)-PEO, chemical cross-linking of modified poly(vinyl alcohol) (PVA), Poly (4vinylpyridine), PEG.

[00113] The analyte sensor further comprises at least one exposed area of the first silver layer, wherein the at least one exposed area is disposed on the exterior of the sensor and configured to be in direct contact with body fluid when the sensor is implanted in a user. Preferably, the sensor comprises a plurality of the exposed areas, and more preferably comprises at least one such exposed area on each lateral side of the sensor. Preferably, the second silver layer is not exposed (i.e., is disposed only on the interior of the sensor and is not disposed on the exterior of the sensor and is not configured to be in direct contact with body fluid when the sensor is implanted in a user) and only has indirect contact to the body fluid via the first silver layer in implanted sensors.

[00114] Another aspect of the present invention is a method for manufacturing an analyte sensor, in particular the ~~inventive~~ analyte sensor, the method comprising the steps:

a) providing a raw substrate which comprises a first side and a second side,

b) preparing a working electrode region on the first side of the raw substrate, the preparing of the working electrode region comprising the steps:

   b1) applying an electrically conductive material to the first side of the raw substrate,

   b2) applying a sensing material comprising at least one enzyme at least partially on the electrically conductive material,

c) preparing a second electrode region on the second side of the raw substrate, the preparing of the second electrode region comprising the steps:

   c1) applying a first silver composition to form a first silver composition region on the second side of the raw substrate,

   c2) applying a second silver composition as a plurality of separated regions over the first silver composition region such that the second silver composition regions at least partially overlap with the first silver composition region, wherein the second silver composition has a different composition than the first silver composition,

d) applying a polymer composition on top of the second electrode region, to obtain a membrane, wherein the polymer composition comprises a hydrophobic polymer,

e) cutting the raw substrate, the working electrode region, the second electrode region and the membrane, wherein only the first silver composition region of the second electrode region is cut, to obtain the analyte sensor.

[00115] Process steps a) to e) may be carried out in the given order. However, it is also possible to carry out the steps in different orders. In particular, the order of steps b) and c) may be different. It is even possible, to first carry out step b1), then step c1) and thereafter step b2), for example. Further process steps are feasible. It is also possible to carry out at least one of process steps a) to e) more than once. For example, step c1) may be carried our more than once, so that more than one layer of the silver composition is obtained. Furthermore, step c2) can be carried out in successive steps, simultaneous steps, or a combination thereof, wherein a plurality of second silver composition regions are applied.

[00116] In step a) of the method for manufacturing the ~~inventive~~ analyte sensor, a raw substrate is provided.

[00117] Within the context of the present invention, the term "raw substrate" specifically may refer, without limitation, to any kind of material or combination of materials which is suitable to form a carrier layer to support the at least one working electrode and the at least one second electrode. From the raw substrate, the substrate of the ~~inventive~~ analyte sensor may be manufactured, for example, by cutting the raw substrate. In particular, the raw substrate may comprise an electrically insulating material. For the electrically insulating material, the embodiments and preferences described above for the electrically insulating material of the substrate hold true.

[00118] Thus, in a preferred embodiment the raw substrate comprises at least one electrically insulating material selected from the group consisting of an insulating epoxy resin, a polycarbonate, a polyester, a polyvinylchloride, a polyurethane, a polyether, a polyethylene, a polyamide, a polyimide, a polyacrylate, a polymethacrylate, a polytetrafluoroethylene or a copolymer thereof, and alumina.

[00119] A suitable polyester is for example polyethylene terephthalate.

[00142] The second electrically conductive material can be applied to the first side of the raw substrate by any known method, for example via chemical vapor deposition (CVD), physical vapor deposition (PVD), or a wet-coating process. Wet-coating processes are known as such. A suitable wet-coating process is for example selected from the group consisting of spin-coating, spray-coating, doctor-blading, printing, dispensing, slot-coating, dip coating and screen printing.

[00143] In step c2) a second silver composition is applied as a plurality of separated regions over the first silver composition region such that the second silver composition regions at least partially overlap with the first silver composition region, wherein the second silver composition has a different composition than the first silver composition. The plurality of separated regions ultimately form the second silver layers of finished analyte sensors. In a preferred embodiment, the first silver composition and the second silver composition each comprise AgCl and the second silver composition comprises a higher weight percent of AgCl than the first silver composition based on the total weight of the first silver composition and the total weight of the second silver composition.

[00144] In step d) a polymer composition is applied on top of the second electrode region as another continuous coating completely covering both previously coated layers to form the membrane. For the polymer composition, the embodiments and preferences described above hold true.

[00145] In an embodiment, during the ~~inventive~~ process no polymer composition which comprises a hydrophobic polymer is applied to the first side of the substrate.

[00146] The polymer composition may be applied on top of the second electrode region by any method known, for example by a wet-coating process. A suitable wet-coating process is for example selected from the group consisting of spin-coating, spray-coating, doctor-blading, printing, dispensing, slot-coating, dip coating and screen printing. After the wet-coating process, the layer of the polymer composition may be further treated. Such treatments are for example drying treatments, curing treatments and/or laser ablation treatments. Such treatments are known as such.

[00147] In step e) the raw substrate, the working electrode region, the second electrode region and the membrane are cut, wherein only the first silver composition region of the second electrode region is cut, to obtain the analyte sensor. In other words, the second silver composition region is not cut in step

e). The cutting (sensor separation) takes place along a line where only the first silver layer of the second electrode is present. Preferably, the cutting is carried out such that a plurality of exposed areas of the first silver composition region are formed in the separated sensors, with two such exposed areas preferably being formed, typically on the lateral edges of each cut sensor.

[00148] The cutting in step e) is carried out such that analyte sensor strips are formed. These strips may correspond to the analyte sensors. It is also possible that, before or after the raw substrate is cut as described above, that the raw substrate is cut at least once along its other dimension.

[00149] Preferably in the method for manufacturing an analyte sensor as described herein, the cutting in step e) comprises laser-cutting.

[00150] Further process steps may be carried out. For example, in a step f) a flux limiting membrane may be applied.

[00151] Thus, in an embodiment of the ~~inventive~~ method the following step f) is carried out:

f) applying a flux limiting membrane to the analyte sensor obtained in step e) to obtain a covered analyte sensor.

[00152] For the flux limiting membrane, the preferences and embodiments described above hold true. In particular, the flux limiting membrane, preferably the at least one polymeric material comprised in the flux limiting membrane, may for example be applied by a wet-coating process. A suitable wet-coating process is for example selected from the group consisting of spin-coating, spray-coating, doctor-blading, printing, dispensing, slot-coating, dip coating and screen printing.

[00153] As a further example, in a step g) a biocompatibility membrane may be applied.

[00154] Thus, in an embodiment of the ~~inventive~~ method, the following step g) is carried out:

g) applying a biocompatibility membrane to the analyte sensor obtained in step e)

[00155] If step f) is carried out, then the biocompatibility membrane is typically applied to the covered analyte sensor obtained in step f)

[00156] Thus, in case step f) is carried out, in an embodiment the following step g) is carried out:

g) applying a biocompatibility membrane to the covered analyte sensor obtained in step f)

[00157] For the biocompatibility membrane, the preferences and embodiments described above hold true. In particular, the biocompatibility membrane usually consists of a biocompatible material. Thus, preferably, in step g) a biocompatible material is applied. The biocompatibility membrane, preferably the biocompatible material may be applied by any process known, in particular by a wet-coating process. A suitable wet-coating process is for example selected from the group consisting of spin-coating, spray-coating, doctor-blading, printing, dispensing, slot-coating, dip coating and screen printing.

[00158] Another aspect of the present invention is, therefore, also an analyte sensor obtainable by the ~~inventive~~ method for manufacturing an analyte sensor.

[00159] A further aspect of the present invention is an analyte sensor system comprising:

- the ~~inventive~~ analyte sensor and
- an electronics unit, the electronics unit being configured to be electronically connected to the analyte sensor.

[00160] For the analyte sensor comprised in the analyte sensor system, the embodiments and preferences described above for the ~~inventive~~ analyte sensor hold true.

[00161] The term “electronics unit” as used herein is a broad term and is to be given its ordinary and customary meaning to a person of ordinary skill in the art and is not to be limited to a special or customized meaning. The term specifically may refer, without limitation, to a unit, such as a unit which may be handled as a single piece, which is configured for performing at least one electronic function. Specifically, the electronics unit may have at least one interface for being connected to the analyte sensor, wherein the electronics unit may provide at least one electronic function interacting with the analyte sensor, such as at least one measurement function. The electronics unit specifically may be

Claims

What is claimed is:

1. An analyte sensor comprising
- a substrate comprising a first side and a second side;
- at least one working electrode positioned on the first side of the substrate, the at least one working electrode comprising:
    - at least one electrically conductive material and
    - at least one enzyme;
- at least one second electrode positioned on the second side of the substrate, the at least one second electrode comprising at least one first silver layer and at least one second silver layer, wherein the second silver layer at least partially overlaps with the first silver layer, wherein the first and second silver layers comprise different compositions, wherein the first and the second silver layers comprise AgCl and wherein the first silver layer includes a lower weight % of AgCl than the weight % of AgCl of the second silver layer based on the total weight of the first silver layer and the total weight of the second silver layer; and
- a membrane comprising a polymer composition which comprises a hydrophobic polymer, wherein the membrane is located on top of the at least one second electrode,
- wherein the sensor comprises at least one exposed area of the first silver layer, said at least one exposed area being disposed on the exterior of the sensor and configured to be in direct contact with body fluid when the sensor is implanted in a user.

2. The analyte sensor according to claim 1, wherein the analyte sensor is an implantable sensor.

3. The analyte sensor according to claim 1 or 2, wherein the at least one second electrode is selected from the group consisting of a counter electrode, a reference electrode and a combined counter/reference electrode.

4. The analyte sensor according to any one of claims 1 to 3, wherein the first side and the second side of the substrate are positioned opposite each other.

5. The analyte sensor according to any one of claims 1 to 4, wherein the at least one second electrode comprises Ag and/or AgCl.

~~6. The analyte sensor according to any one of claims 1 to 5 wherein the first and the second silver layers comprise AgCl and wherein the first silver layer includes a lower weight % of AgCl than the weight % of AgCl of the second silver layer based on the total weight of the first silver layer and the total weight of the second silver layer.~~

~~7.~~6. The analyte sensor according to any one of claims 1 to ~~6~~ 5 wherein the first silver layer comprises in the range from 50 to 99 wt.-% of Ag, in the range from 0 to 30 wt.-% of AgCl and in the range from 1 to 20 wt.-% of a binder based on the applied and dry layer weight percentages of the total weight of the first silver layer.

~~8.~~7. The analyte sensor according to any one of claims 1 to ~~7~~ 6 wherein the second silver layer comprises in the range from 0 to 59 wt.-% of Ag, in the range from 40 to 99 wt.-% of AgCl, and in the range from 1 to 20 wt.-% of a binder based on the applied and dry layer weight percentages of the total weight of the second silver layer.

~~9.~~8. The analyte sensor according to any one of claims 1 to ~~8~~7, wherein the at least one second electrode comprises AgCl having a load in the range from 20 µg to 150 µg.

~~10.~~9. The analyte sensor according to any one of claims 1 to ~~9~~8, wherein the sensor comprises two of the exposed areas.

~~11.~~10. The analyte sensor according to any one of claims 1 to ~~10~~9, wherein the second silver layer is disposed only on the interior of the sensor and is not disposed on the exterior of the sensor and is not configured to be in direct contact with body fluid when the sensor is implanted in a user.

~~12.~~11. A method for manufacturing an analyte sensor, the method comprising the steps:

a) providing a raw substrate which comprises a first side and a second side;

b) preparing a working electrode region on the first side of the raw substrate, the preparing of the working electrode region comprising the steps:

   b1) applying an electrically conductive material to the first side of the raw substrate,

   b2) applying a sensing material comprising at least one enzyme at least partially on the electrically conductive material;

c) preparing a second electrode region on the second side of the raw substrate, the preparing of the second electrode region comprising the steps:

c1) applying a first silver composition to form a first silver composition region on the second side of the raw substrate,

c2) applying a second silver composition as a plurality of separated regions over the first silver composition region such that the second silver composition regions ~~at least~~ partially overlap with the first silver composition region, wherein the second silver composition has a different composition than the first silver composition, wherein the first silver composition and the second silver composition each comprise AgCl and the first silver composition includes a lower weight % of AgCl than the second silver composition based on the total weight of the first silver composition and the total weight of the second silver composition;

d) applying a polymer composition on top of the second electrode region, to obtain a membrane, wherein the polymer composition comprises a hydrophobic polymer; and

e) cutting the raw substrate, the working electrode region, the second electrode region and the membrane, wherein only the first silver composition region of the second electrode region is cut such that the first silver composition region comprises at least one exposed area configured to be in direct contact with body fluid when the sensor is implanted in a user.

~~13.~~12. The method according to claim ~~12~~11, wherein the cutting in step e) comprises cutting such that a plurality of the exposed areas of the first silver composition region are formed.

~~14. The method according to claim 12 or 13, wherein the first silver composition and the second silver composition each comprise AgCl and the first silver composition includes a lower weight % of AgCl than the second silver composition based on the total weight of the first silver composition and the total weight of the second silver composition.~~

~~15.~~13. The method according to any one of claims ~~12~~11 ~~to 14~~ or 12, wherein the cutting in step e) comprises laser-cutting.

~~16.~~14. The method according to any one of claims ~~12~~11 to ~~15~~13, further comprising a step f): applying a flux limiting membrane to the analyte sensor obtained in step e) to obtain the analyte sensor.

~~17.~~15. The method according to claim ~~16~~14, further comprising a step g): applying a biocompatibility membrane to the analyte sensor obtained in step f) to obtain the analyte sensor.

~~18.~~16. An analyte sensor system comprising

- the~~an~~ analyte sensor according to any one of claims 1 to ~~11~~10 or the~~an~~ analyte sensor obtained by the method according to any one of claims ~~12~~11 to ~~17~~15; and
- an electronics unit, the electronics unit being configured to be electronically connected to the analyte sensor.