Roche Diagnostics GmbH
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RD26962PC ST/RZ/sj

Analytical aid with hydrophilic coating that contains nanoparticles with a silicon dioxide structure

Field of the invention

The present invention relates to an analytical aid, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008 (dynamic light scattering), in the range from 1 to 500 nm. The present invention further relates to a method of production of an analytical aid, comprising a surface coated at least partially with a hydrophilic coating containing nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008 (dynamic light scattering), in the range from 1 to 500 nm. The present invention also relates to an analytical aid producible by this method and a sampling device containing the at least partially coated analytical aid described.

Prior art

A great many analytical aids are described in the prior art, in particular for the rapid and quantitative analytical determination of constituents of liquid samples, for example in the form of individual test strips or strip-shaped test materials or in integrated systems, in which the testing element is a part of a sampling device. For reasons of simplified and more economical production and component stability, conventional testing elements are as a rule made of plastic or metal and generally have a comparatively hydrophobic surface, which is a disadvantage for rapid and uniform wetting of the analytical aid with the liquid, generally aqueous, samples.

Thus, for example from WO 2007/045412, sampling devices for collecting body fluids are known, which have a needle element and are equipped with a testing element, with which at least one analyte in the body fluid can be detected qualitatively or quantitatively. In this case the sample of body fluid is transported along the needle element to the testing element. Since as a rule the site of insertion of the needle element in the skin is disposed at some distance from the testing element, as a rule the sample of body fluid must travel a few millimetres along the capillary to reach the testing element. Usually needle elements made of steel are used, which have a relatively hydrophobic steel surface, and therefore are not very suitable for transporting the aqueous body fluid.

For the purpose of increasing the flow rate of the body fluid along the needle element, EP 2 025 287 A1 describes modification of the surface of the needle element with a hydrophilic coating. Non-ionic surfactants, such as polysorbate, are mentioned in particular as hydrophilic coatings.

Similarly, EP 2 014 727 A1 describes hydrophilizing metal-oxide coatings, for example AlOOH, TiO_X, SiO_2, or the like, wherein these coatings are for example applied and fixed in the form of discrete particles in suspensions. The use of organic polymer compounds, for example PVP-PEG, and of water-soluble organic poly-acids and/or salts thereof, for example PAA or heparin salts, as hydrophilic coating, is also known from the prior art.

For forming a hydrophilic surface of the needle element, a hydrophilization by physicochemical means is also possible, for example the etching of a steel surface or a plasma or corona treatment in the sense of creating active metal surfaces. Usually these effects are temporary and therefore as a rule are only auxiliary measures for preparing the needle element surface for subsequent coating.

In order to improve the transport of the body fluid along the needle element, in addition a capillary-active surface structure can be provided, and hydrophilic coating of precisely this capillary surface structure can be especially advantageous for the speed of transport of the body fluid along the needle element.

EP 1 887 355 A1 describes a needle element designed as a microfluidic system for the capillary transport of a liquid and a method of applying a hydrophilic surface coating on said needle element. Polyacrylic acid, polyacrylate, dextran sulphate and/or chondroitin sulphate are used as surface coating materials. Especially preferably, a surface structure formed as a microchannel on the needle element is provided with said hydrophilic surface coating, to ensure rapid and reliable transport of the body fluid along the needle element.

However, the coating materials described in the prior art often have inadequate stability, in particular inadequate long-term stability. As reasons for inadequate stability, we may mention for example insufficient bonding of the coating to the coated surface of the substrate, which may result in detachment of the coating during the coating process, or during storage or during use of the substrate, for example when a needle element coated in this way is inserted into the skin. The hydrophilic coating may also not even be resistant to longer storage at room temperature or to temperature fluctuations. Moreover, some compounds display low stability when they are exposed to sterilization conditions and/or low resistance to gas evolution from packaging.

In particular, instability with respect to packaging materials often means that, for example in the case of substrates packaged in plastic materials, the hydrophilicity of the coated surfaces decreases markedly during storage and sufficient hydrophilicity of the substrates after storage is no longer guaranteed. This loss of hydrophilicity can for example be explained by adsorption of volatile, as a rule nonpolar, constituents of the packaging materials.

In order to prevent such loss of hydrophilicity, WO 2008/015227 describes the use of specific packaging, which contains a loose covering for the hydrophilic coating and/or the addition of adsorbents in the packaging, to prevent absorption of said volatile constituents by the hydrophilic coating. However, the packaging proposed in WO 2008/015227 is complicated, expensive and in particular is disadvantageous for measuring equipment with automatic operation, which must also provide reliable unpacking of the substrate from the packaging.

US 20070179373 A1 describes apparatus and methods for collecting a fluid sample. It discloses inter alia an integrated collection device having an analyte detector and a gradient means to drive the transport of a sample fluid from a point of contact to a point of detection. The integrated collection device has a layered structure including multiple layers. The design features inter alia a first layer and a second layer which forms a surface layer. A hydrophilic surface is generated by powder coating with fumed silica nanoparticles.

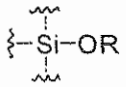
There is therefore a need for analytical aids with hydrophilic coatings, which have sufficient stability, in particular sufficient stability even in the presence of volatile, as a rule nonpolar, constituents of packaging materials.

The problem to be solved by the invention

The present invention is therefore concerned with the problem of providing an analytical aid with a hydrophilic coating, which has advantageous wetting properties and is characterized by high stability of the coating.

Summary

In one aspect, there is provided an analytical aid, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm and the nanoparticles comprise groups of structure (I) or (II)



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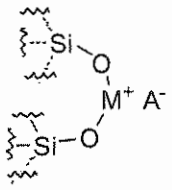

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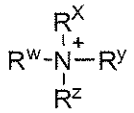
wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



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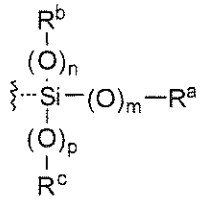


and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

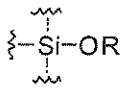
and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

In another aspect, there is provided a method of production of an analytical aid, comprising a surface that is coated at least partially with a hydrophilic coating, wherein the method comprises:

(a) providing the analytical aid,

(b) coating the analytical aid by bringing the analytical aid into contact with a mixture G comprising at least one dispersant and nanoparticles with silica structure, which have an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm,

wherein the nanoparticles comprise groups of structure (I) or (II)



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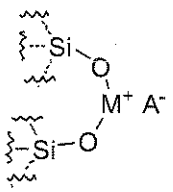

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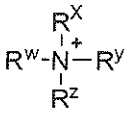
wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



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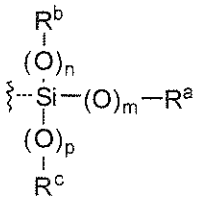


and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion,

(c) drying the analytical aid obtained according to (b), and

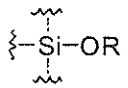
(d) optionally sterilizing the analytical aid obtained according to (c),

wherein the bringing into contact in (b) preferably takes place by dip coating and/or spray coating and/or contact coating, and wherein the analytical aid and/or the surface of the analytical aid preferably consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

In another aspect, there is provided an analytical aid, producible or produced by a method as defined above.

In another aspect, there is provided a sampling device for taking a sample of body fluid, containing at least one analytical aid as defined above referring to an analytical aid, with the proviso that the analytical aid is selected from the group consisting of a needle element and a testing element.

In another aspect, there is provided the use of nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm as hydrophilic coating for a surface of an analytical aid, more preferably as hydrophilic coating for a needle element of a sampling device for taking a sample of body fluid, wherein the nanoparticles comprise groups of structure (I) or (II)



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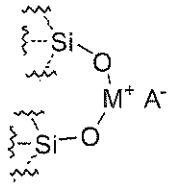
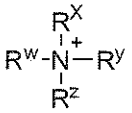


(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



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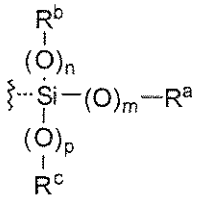


and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

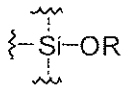
Disclosure of the invention

According to the invention, this problem is solved by the objects of the independent claims. Advantageous embodiments are the object of the dependent claims.

Surprisingly, it was found that when nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008 (dynamic light scattering), in the range from 1 to 500 nm are used for coating analytical aids, analytical aids with especially advantageous properties are produced. The analytical aids so coated are characterized by advantageous hydrophilicity and wettability. Moreover, high stability of the coating is provided.

Accordingly, the present invention also relates to an analytical aid, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating

contains nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008 (dynamic light scattering), in the range from 1 to 500 nm, and the nanoparticles comprise groups of structure (I) and/or (II)



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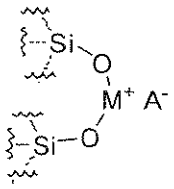

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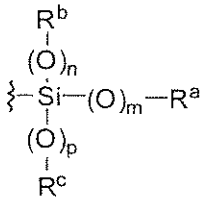

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and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

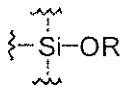
and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

In contrast, for example, to the abovementioned US 20070179373 A1, which discloses only a hydrophilic surface coating with fumed silica nanoparticles, the nanoparticles provided in accordance with the invention thus comprise groups of structure (I) and/or (II).

The present invention also relates to a method of production of an analytical aid, comprising a surface that is coated at least partially with a hydrophilic coating, wherein the method comprises:

(a) providing the analytical aid,

(b) coating the analytical aid by bringing the analytical aid into contact with a mixture G comprising at least one dispersant and nanoparticles with silica structure, which have an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm,
wherein the nanoparticles comprise groups of structure (I) and/or (II)



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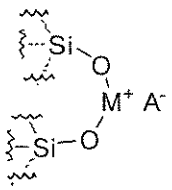

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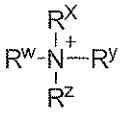
wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



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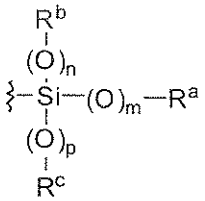


,

and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

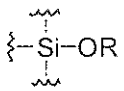
and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

(c) drying the analytical aid obtained according to (b), and

(d) optionally sterilizing the analytical aid obtained according to (c),

wherein the bringing into contact in (b) preferably takes place by dip coating and/or spray coating and/or contact coating, and wherein the analytical aid and/or the surface of the analytical aid preferably consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

According to another embodiment, the present invention also relates to the use of nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008 (dynamic light scattering), in the range from 1 to 500 nm as hydrophilic coating for a surface of an analytical aid, preferably as hydrophilic coating for a needle element of a sampling device for collecting a body fluid, wherein the nanoparticles comprise groups of structure (I) and/or (II)



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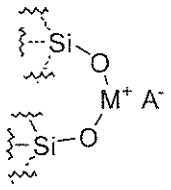
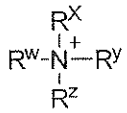


(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



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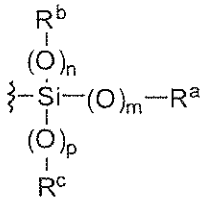


and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl, and wherein n, m and p, independently of one another, are 0 or 1, and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

Nanoparticles

As already noted, the coating comprises nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008 (dynamic light scattering), in the range from 1 to 500 nm.

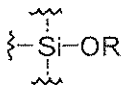
Preferably the nanoparticles have a size in the range from 1 to 100 nm, more preferably in the range from 1 to 50 nm, more preferably in the range from 3 nm to 25 nm, and especially preferably in the range from 5 to 15 nm.

The nanoparticles preferably have a BET surface area in the range from 100 to 700 m^2/g.

The coating has preferably an average layer thickness, also referred to as average thickness or mean thickness hereinbelow, of no more than 500 nm, for example no more than 300 nm. The layer thickness may be measured by common methods, for example by means of a destructive or a non-destructive method. More specifically, the layer thickness may be

measured by means of an ellipsometer and/or by means of a scanning force microscope and/or by means of an "alpha stepper", that is a device which scans a surface of the layer by means of a stylus, the deflection and/or position of which is recorded. Other measurement methods are also conceivable. Alternatively or additionally, the average layer thickness may furthermore also be calculated and/or determined semi-empirically. For example, the average layer thickness may be determined from a known thickness of the coating and a coating weight. Thus, for example, calculated average layer thicknesses may be in the range from 30 nm to 300 nm, in particular in the range from 50 nm to 150 nm. Fluctuations, for example fluctuations in one or more channels and/or capillaries and/or fluctuations due to edge effects, need not be taken into account here.

With regard to the structure of the nanoparticles, as noted above, they are nanoparticles with silica structure, which comprise groups of structure (I) and/or (II)



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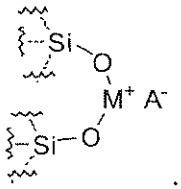


(II)

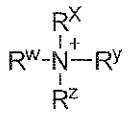
Preferably at least a portion of the surface of the nanoparticles is modified with groups of structure (I) or groups of structure (II), preferably at least with groups of structure (I).

According to a preferred embodiment, the present invention accordingly relates to an analytical aid, as described above, comprising at least one surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, which comprise groups of structure (I). The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at

least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles have groups of structure (I).

Groups of structure (I)

As mentioned above, the residue R is selected from the group consisting of H, a metal-containing ion,



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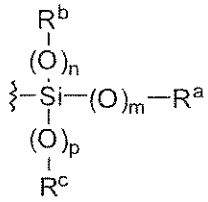
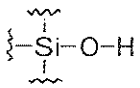


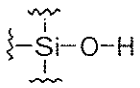
wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl, and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl, and wherein n, m and p, independently of one another, are 0 or 1.

When R is H, the silica particles then preferably comprise groups of structure



.

Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, which comprise groups of structure



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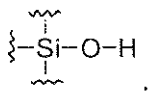
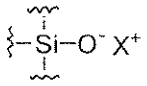
The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b)

with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles have groups of structure

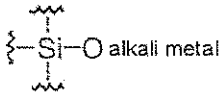


According to an alternative embodiment, R is a metal-containing ion. In this case the silica particles therefore preferably contain groups of structure

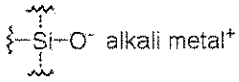


According to a preferred embodiment, X^+ is an alkaline-earth metal containing ion, such as Mg^{2+} or Ca^{2+}, an alkali metal ion or an aluminium containing ion.

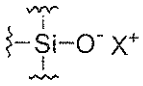
When R is an alkali metal ion, the nanoparticle then preferably comprises groups of structure



or the structure:



Especially preferably, the alkali metal is selected from the group consisting of Li^+, Na^+, K^+ and mixtures thereof. In this context, the term "mixtures thereof" means that in each individual group of structure



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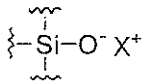
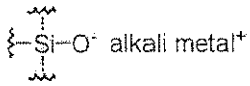
X^+, independently of each X^+ contained in each further group of structure Si-O- X^+ contained in the silicon nanoparticle, is selected from the group consisting of

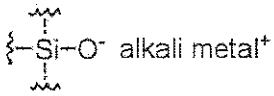


containing X^+ is selected from the group consisting of Li^+, Na^+ and K^+, and therefore the nanoparticles can in each case have several different alkali metal counter-ions. Quite especially preferably, X^+ is Na^+.

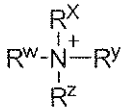
Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, which comprise groups of structure



The present invention also relates to a method of production of an analytical aid and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles have groups of structure



According to an alternative embodiment, R is a cation of the following structure

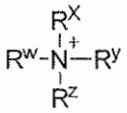


wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl.

The term "alkyl", as used in the context of the present invention, means linear or branched, optionally substituted alkyl residues.

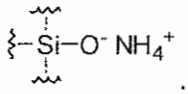
If R^w and/or R^x and/or R^y and/or R^z is an alkyl residue, it is preferably an alkyl residue selected from the group consisting of methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl and tert.-butyl, preferably methyl.

If R is

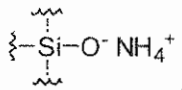


then R^w, R^x, R^y and R^z especially preferably, independently of one another, are selected from H, methyl and ethyl. Especially preferably, R^w, R^x, R^y and R^z are H.

Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, which comprise groups of structure

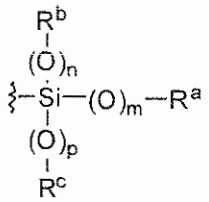


The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles have groups of structure



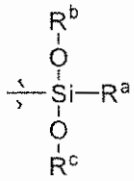
Said nanoparticles are obtainable for example under the name Ludox® AS-30 (Grace, Aldrich) or Levasil® 200N/30%. (EKA).

According to an especially preferred embodiment of the present invention, R is



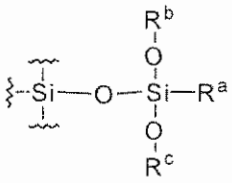
and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl, and wherein n, m and p, independently of one another, are 0 or 1.

According to a preferred embodiment of the invention, R is

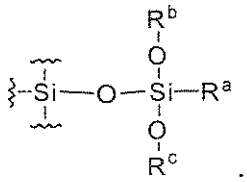


wherein p and n are 1 and m is 0.

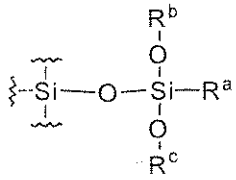
Accordingly, the present invention also relates to an analytical aid as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, which comprise silane-modified silicon groups of structure



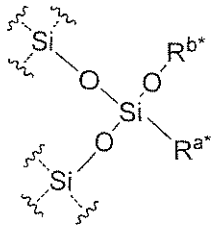
The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles have silane-modified silicon groups of structure



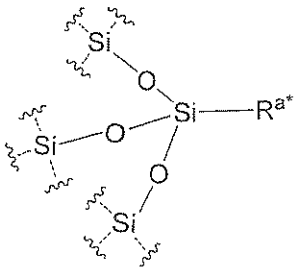
If the silicon nanoparticles contain silane-modified silicon groups of structure



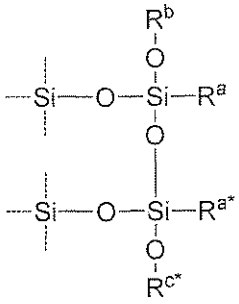
then the silicon nanoparticles can optionally contain further modification of silane groups, for example groups of structure



and/or groups of structure



and/or groups of structure



and/or similar branched modifications of silane groups,

in which R^{a*}, R^{b*} and R^{c*}, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl.

The term "substituted alkyl residue", as used in the context of the present invention, means alkyl residues in which at least one H has been replaced with a suitable substituent. A substituted alkyl residue can contain at least one, for example 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 substituents, wherein, if more than one substituent is present, the substituents present can be identical or different. With regard to the nature of the substituents, in principle there are no restrictions, provided that when the nanoparticles are used, a coating with sufficient hydrophilicity and stability can be provided. The substituents can for example be selected from the group consisting of epoxy, aryl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, phosphoric acid ester, amino, acylamino, alkylcarbonylamino, arylcarbonylamino, carbamates, carbamides, amidine, nitro, imino, SH, alkylthio, arylthio, thiocarboxylate, sulphate, alkylsulphinyl, sulphonate, sulphamoyl, sulphonamido, trifluoromethyl, cyano, azido, aldehyde, keto group, cycloalkyl e.g. cyclopentyl or cyclohexyl, heterocycloalkyl e.g. morpholino, piperazinyl or piperidinyl, and glycosyl. Especially preferred substituents are hydroxyl groups, glycosyl groups and phosphoric acid ester groups.

The term "cycloalkyl" means, in the context of the invention, optionally substituted, cyclic alkyl residues, wherein they can be monocyclic or polycyclic groups. Optionally substituted cyclohexyl may be mentioned as a preferred example of a cycloalkyl residue.

The term "cycloheteroalkyl", as used in the context of the present invention, means optionally substituted, cyclic alkyl residues, which have at least one heteroatom, such as O, N or S in the ring, wherein they can be monocyclic or polycyclic groups.

The terms "substituted cycloalkyl residue" or "cycloheteroalkyl", as used in the context of the present invention, mean cycloalkyl residues or cycloheteroalkyl residues, in which at least one H has been replaced with a suitable substituent. A substituted cycloalkyl residue or cycloheteroalkyl residue can in this case contain at least one, for example 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 substituents, wherein, if more than one substituent is present, the substituents present can be identical or different. With regard to the nature of the substituents, reference is made to the substituents mentioned as examples with respect to substituted alkyl residues.

The term "aryl", as used in the context of the present invention, means optionally substituted, 5- and 6-membered aromatic rings, and substituted or unsubstituted polycyclic aromatic groups (aryl groups), for example tricyclic or bicyclic aryl groups. Optionally substituted phenyl groups or naphthyl groups may be mentioned as examples. Polycyclic aromatic groups can also contain non-aromatic rings.

The term "heteroaryl", as used in the context of the present invention, means optionally substituted, 5- and 6-membered aromatic rings, and substituted or unsubstituted polycyclic aromatic groups, for example tricyclic or bicyclic aryl groups, containing one or more, for example 1 to 4, such as 1, 2, 3, or 4, heteroatoms in the ring system. If more than one heteroatom is present in the ring system, the at least two heteroatoms that are present can be identical or different. The following heteroaryl residues may be mentioned as examples: benzodioxolyl, pyrrolyl, furanyl, thiophenyl, thiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrazinyl, pyridazinyl, benzoxazolyl, benzodioxazolyl, benzothiazolyl, benzimidazolyl, benzothiophenyl, methylene-dioxyphenylyl, naphthyridinyl, quinolinyl, isoquinolinyl, indolyl, benzofuranyl, purinyl, benzofuranyl, deazapurinyl or indolizinyl.

The term "substituted aryl residue or heteroaryl residue", as used in the context of the present invention, means aryl residues or heteroaryl residues, in which at least one H has been replaced with a suitable substituent. A substituted aryl residue or heteroaryl residue can in this case contain at least one, for example 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 substituents, wherein, if more than one substituent is present, the substituents present can

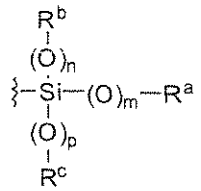
be identical or different. With regard to the nature of the substituents, in principle there are no restrictions, provided that compound M has sufficient hydrophilicity and/or a sufficiently stable coating can be provided with compound M. The substituents can for example be selected from the group consisting of aryl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, phosphoric acid ester, amino, acylamino, alkylcarbonylamino, arylcarbonylamino, carbamates, carbamides, amidine, nitro, imino, SH, alkylthio, arylthio, thiocarboxylate, sulphate, alkylsulphinyl, sulphonate, sulphamoyl, sulphonamido, trifluoromethyl, cyano, azido, cycloalkyl e.g. cyclopentyl or cyclohexyl, heterocycloalkyl e.g. morpholino, piperazinyl or piperidinyl, sugar residues and heteroaryl.

The term "alkoxyalkyl" means alkyl residues that comprise one or more –O- groups within the alkyl chain. The term comprises groups of alkyl-O-alkyl structure and similar structures, wherein the respective alkyl residues, as described above, can be substituted or unsubstituted.

The term alkenyl means alkyl residues that have at least one C-C double bond. Regarding the nature of possible substituents, reference is to be made to the foregoing.

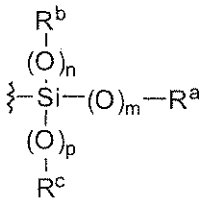
According to a preferred embodiment of the invention, R^a, R^b and R^c are selected, independently of one another, from the group consisting of H, optionally substituted alkyl residues and optionally substituted alkyoxyalkyl residues.

Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, which comprise groups of structure (I), wherein R is



and wherein R^a, R^b and R^c, independently of one another, are selected from the group consisting of H, optionally substituted alkyl residues and optionally substituted alkyoxyalkyl residues.

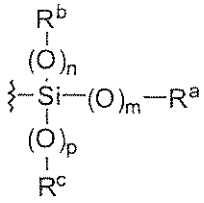
The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles comprise groups of structure (I), wherein R is



and wherein R^a, R^b and R^c, independently of one another, are selected from the group consisting of H, optionally substituted alkyl residues and optionally substituted alkyloxyalkyl residues.

The following preferred groups may be mentioned as examples of the residues R^a, R^b or R^c:

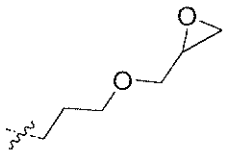
Examples of silica nanoparticles modified with groups of structure

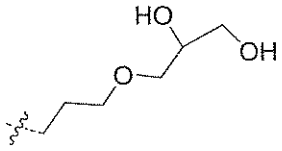


are those that are for example modified with the following silanes: octyltriethoxysilane, methyltrimethoxysilane, methyltriethoxysilane, methyltriisopropoxysilane, isocyanate

silane, beta-(3,4-epoxycyclohexyl)-ethyl-trimethoxysilane; epoxy-silanes or silanes that have a glycidoxy- and/or a glycidoxypropyl group, such as gamma-glycidoxypropyltrimethoxysilane, gamma-glycidoxypropyltriethoxysilane, gamma-glycidoxypropylmethyldiethoxysilane, 3-glycidoxypropyl-hexyltrimethoxysilane, beta-(3,4-epoxycyclohexyl)-ethyltriethoxysilane, silanes that contain a vinyl group, such as vinyltriethoxysilane, anhydride silanes, i.e. silanes that bear a cyclic organic anhydride unit e.g. succinic anhydride or maleic acid anhydride, and hydrolysis products thereof, and/or aminosilanes such as 3-aminopropyltri(m)ethoxysilane and di-triaminosilanes.

Especially preferably, R^a, R^b and R^c, independently of one another, are selected from the group consisting of H, alkyl and groups of the following formulae:

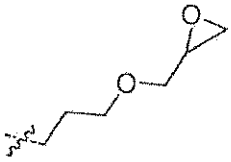




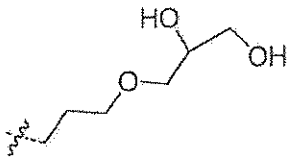
,

wherein the alkyl group is more preferably methyl or ethyl, and especially preferably is ethyl.

Quite especially preferably, p and n are 1 and m = 0 and R^b and R^c are methyl or ethyl, preferably, ethyl, and R^c is more preferably



or



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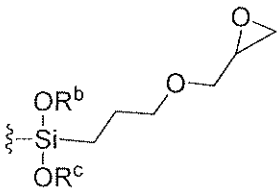
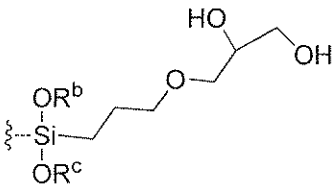
Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, wherein the group of formula (I) has a structure of formula (Ia) or (Ib):

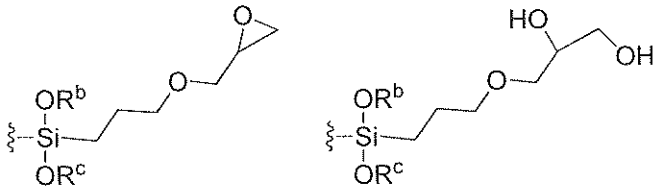




.

(Ia) (Ib)

The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the group of formula (I) has a structure of formula (Ia) or (Ib):

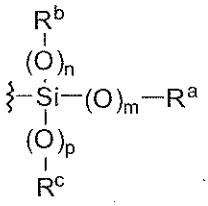


(Ia) (Ib)

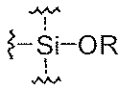
and wherein R^b and R^c, independently of one another, are selected from the group consisting of H and alkyl, preferably H, methyl and ethyl.

Said nanoparticles are obtainable for example under the name Bindzil® CC30 or CC301 and CC40 or CC401 (EKA Akzo Nobel).

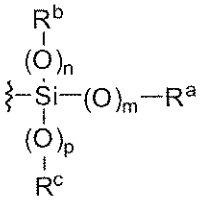
If the nanoparticles contain groups of formula (I), in which R is



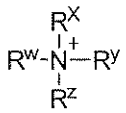
then preferably 10 to 50% of all groups R of the groups present in the silicon nanoparticle



have the structure of formula

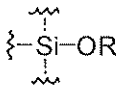


The remaining 50% to 90% of the groups R contained in the nanoparticle are H and/or a metal-containing ion and/or

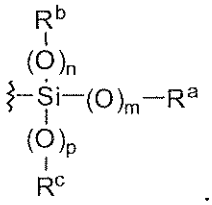


depending on which counter-ion was used for stabilizing the nanoparticles. Preferably, the remaining groups R, as described above, are H and/or Na^+.

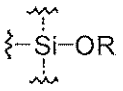
Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, which comprise groups of structure



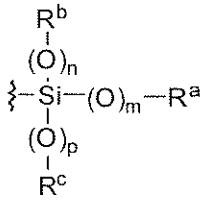
wherein preferably 5 to 50% of all groups R have a structure of formula



The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles have groups of structure

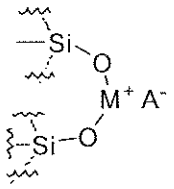


and wherein preferably 5 to 50% of all groups R have a structure of formula



Groups of structure (II)

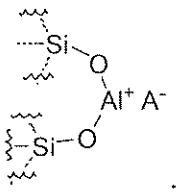
According to another embodiment of the invention, the silica nanoparticles have, additionally or alternatively to the groups of formula (I), groups of formula (II)



In particular, the nanoparticles have either groups of formula (I) or groups of formula (II), i.e. when the nanoparticles have groups of formula (I), preferably they have no groups of formula (II), and vice versa.

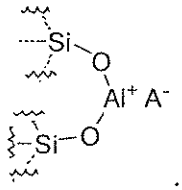
M is a metal, preferably a trivalent metal, more preferably aluminium. Especially preferably, M is accordingly aluminium or $M^+ = Al^+$.

Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure and the nanoparticles comprise groups of structure (IIa)



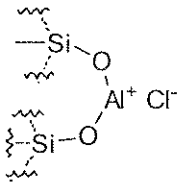
The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b)

with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles comprise groups of structure (IIa)

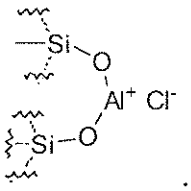


With regard to the chemical nature of the anion A^-, there are no restrictions in this respect, provided that the anion is physiologically compatible and does not falsify the result when the analytical aid is used. Preferred anions are for example chloride, bromide, iodide, sulphate, hydrogen sulphate, phosphate and hydrogen phosphate. Especially preferably, A^- is chloride.

Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure and the nanoparticles comprise groups of structure (IIa)



The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the nanoparticles comprise groups of structure (IIa)



Nanoparticles containing groups of structure (IIa) are obtained for example by treatment of nanoparticles with aluminium chloride. Such nanoparticles are obtainable for example as Bindzil® CAT (Akzo Nobel).

Silica structure

The nanoparticles have a silica structure, wherein it is preferably amorphous silica. Furthermore, in addition to Si and O and the groups R or M^+, the nanoparticles can have further foreign atoms. These foreign atoms can be for example Sn, Ti, Zr, Hf, Ge, In, Ga, P, Al or B. If present, the foreign atoms replace one or more Si atoms in the silica structure.

According to one embodiment of the invention, the nanoparticles contain aluminium as foreign ion.

Accordingly, the present invention also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, wherein the silica structure of the nanoparticles has at least one foreign atom, selected from the group consisting of Sn, Ti, Zr, Hf, Ge, In, Ga, P, Al and B, preferably wherein the foreign atom is Al.

The present invention also relates to a method of production of an analytical aid, and an analytical aid producible by said method, wherein the analytical aid is coated in step (b) with a mixture G comprising at least one dispersant and nanoparticles with silica structure, as described above, wherein the silica structure of the nanoparticles has at least one foreign atom, selected from the group consisting of Sn, Ti, Zr, Hf, Ge, In, Ga, P, Al and B, preferably wherein the foreign atom is Al.

If the silica structure of the nanoparticles contains at least aluminium, then the nanoparticles contain aluminium preferably in an amount in the range from 0.1 to 10 wt.%, relative to the total weight of the nanoparticle.

Methods of production of the analytical aid

Regarding the coating of the analytical aid by bringing the analytical aid into contact with mixture G in step (b) of the method described above, said coating can be carried out by all methods known by a person skilled in the art. The bringing into contact preferably takes place by dip coating and/or spray coating and/or contact coating. Alternatively or additionally, however, numerous other methods may be considered. For example, a method can be applied, selected from: dip coating, spray coating, spin coating, a pressing process, a knife process or a dropping process. However, combinations of the stated methods and/or other methods can basically also be used.

Mixture G

Regarding the mixture used in step (b), G contains, as described above, in addition to nanoparticles, at least one dispersant. The nanoparticles are preferably dispersed or are in the form of a colloidal solution in the at least one dispersant.

The at least one dispersant is preferably water.

Mixture G can furthermore contain at least one solvent, for example at least one organic solvent, preferably a polar organic solvent, more preferably a polar, protic organic solvent, more preferably an alcohol. According to a preferred embodiment, the at least one organic solvent is miscible with water. Especially preferably, the at least one organic solvent is a solvent selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol, methoxymethanol, methoxyethanol and ethylene glycol. If G contains at least one organic solvent, the solvent mixture preferably contains at most 50 vol.% of the organic solvent, more preferably in an amount in the range from 0.1 vol.% to 30 vol.%, more preferably in the range from 1 vol.% to 20 vol.%, and especially preferably in the range from 1.5 vol.% to 5 vol.%, relative to the total volume of mixture G.

Accordingly, the present invention also relates to a method of production, as described above, and an analytical aid, producible or produced by said method, wherein mixture G furthermore contains at least one solvent in an amount of at most 50 vol.%.

Regarding the amount of nanoparticles in mixture G, mixture G contains the nanoparticles preferably in an amount in the range from 0.01 wt.% to 5 wt.%, preferably in an amount in the range from 0.02 wt.% to 3 wt.%, more preferably from 0.05 wt.% to 2 wt.%, relative to the total weight of mixture G.

Accordingly, the present invention also relates to a method of production of an analytical aid, as described above, and an analytical aid, producible or produced by this method, wherein mixture G contains the nanoparticles preferably in an amount in the range from 0.01 wt.% to 5 wt.%, relative to the total weight of mixture G.

Preferably mixture G consists essentially of the at least one dispersant and the nanoparticles with silica structure. "Essentially" means that the mixture has further constituents, such as impurities, in an amount of at most 1 wt.%, preferably in an amount of at most 0.1 wt.%.

If the coating in step (b) takes place by dip coating, as described above, the dwell time of the analytical aid immersed in mixture G is preferably max. 5 minutes, more preferably max. 2 minutes, more preferably max. 1 minute, for example in the range from 1 s to 30 s.

The method described above for production of the analytical aid additionally comprises, apart from the steps described above

(c) drying the analytical aid obtained according to (b).

Drying means, in the context of the invention, that dispersant present on the analytical aid and any other solvent present is removed essentially completely, preferably completely. Drying can be carried out in a drying cabinet at a predetermined temperature of preferably 20 to 150 degrees Celsius, especially preferably from 20 to 120 degrees Celsius and quite

especially preferably from 20 to 80 degrees Celsius. Additionally or alternatively to this, drying can take place by flow of a gas, for example air, through the analytical aid.

Alternatively or additionally to this, drying can also take place by storage of the coated analytical aid in air or in an inert atmosphere at a temperature in the range from 20 to 150 degrees Celsius, preferably at a temperature in the range from 20 to 80 degrees Celsius, more preferably at room temperature.

Step (c) can, according to one embodiment of the invention, also include an additional washing step. In this case the analytical aid obtained according to (b) is first dried, as described above, the analytical aid is then washed with a solvent or solvent mixture, preferably with water, wherein washing is preferably carried out for a time of max. 1 minute, for example in the range from 1 s to 30 s. Following this optional washing step, the analytical aid is preferably dried again, wherein in the second drying step, the solvent or solvent mixture that was used for washing and is present on the analytical aid, is removed essentially completely, preferably completely. The drying steps can be carried out in the same way or differently. Preferably, no washing step is carried out in (c).

The analytical aid obtained according to (c), is preferably sterilized in another step (d).

Sterilization preferably uses irradiation with gamma radiation and/or beta radiation. Further possibilities that can be employed alternatively or additionally are steam sterilization and/or autoclaving and/or chemical sterilization, for example with ethylene oxide (EtO). Generally, for example at least one sterilization method can be used, selected from the group consisting of: radiation sterilization, in particular with gamma radiation and/or beta radiation, thermal sterilization, in particular dry thermal sterilization and/or steam sterilization, chemical sterilization with at least one germicidal medium, in particular a gaseous and/or liquid germicidal medium.

For example, the analytical aids according to the invention can be packed in suitable containers, for example plastic bags, wherein packing can be effected for example by heat

sealing. The sterilization according to (d) takes place in particular after packing or heat sealing of the analytical aids, in particular by irradiation with gamma radiation.

Especially preferably, the analytical aid is treated before step (b) with at least one etchant and/or plasma.

Accordingly, the present invention also relates to a method, as described above, and an analytical aid producible or produced by said method, wherein the surface of the analytical aid to be coated is treated before step (b) with at least one etchant and/or with plasma.

According to one embodiment, the analytical aid can be etched with an etchant before, for example shortly before step (b). "Shortly before" means, in the context of the present invention, a time interval preferably not exceeding 12 hours, in particular 8 hours, especially preferably 1 hour and in particular 10 minutes. Thus, for example a freshly etched analytical aid is used in step (b). A freshly etched analytical aid means an analytical aid that has been etched lightly on the surface with an etchant shortly before the treatment with mixture G. It is freshly etched if the time that elapses between the etching of the analytical aid and the treatment of the analytical aid with mixture G is preferably max. 0 to 12 hours, especially preferably 0 to 8 hours and quite especially preferably 0 to 4 hours, in particular even 0 to 1 hour or even not more than 10 minutes. If the respective time limits are observed, we have a freshly etched analytical aid in the sense of the present invention.

The analytical aid, optionally etched and then optionally washed with water, is kept in this interval between etching and coating, preferably for example in water, optionally provided with a stabilizer. Optionally, the analytical aid is dried before step (b). Regarding the conditions for drying, reference should be made to the foregoing. Etching is preferably carried out with an etchant that comprises nitric acid or an iron(III) chloride solution and hydrochloric acid.

If nitric acid is used, preferably 20- to 40-wt.% nitric acid is used, especially preferably 25- to 35-wt.% and quite especially preferably 30- to 34-wt.% nitric acid.

According to another embodiment, the surface to be coated, optionally the surface etched as described above, of the analytical aid is treated with plasma shortly before step (b). Thus, preferably an analytical aid freshly treated with plasma is used in step (b). An analytical aid freshly treated with plasma means an analytical aid that was treated with plasma shortly before the treatment with mixture G. It is freshly treated with plasma if the time interval between treatment of the analytical aid with plasma and treatment of the analytical aid with mixture G is preferably max. 0 to 12 hours, especially preferably 0 to 8 hours and quite especially preferably 0 to 4 hours, in particular even 0 to 1 hour or even not more than 10 minutes.

Hydrophilic coating

The term "hydrophilic coating", as used in the context of the present invention, means a coating whose surface has, in comparison with the uncoated surface of the analytical aid, a smaller contact angle with water, preferably at least 15° smaller, preferably measured according to DIN 55660.2. In principle, measurement according to DIN EN 828:1997 would also be suitable. Preferably the surface of the coating has a contact angle with water of less than 60°, preferably of less than 50°, more preferably of less than 40°, and especially preferably of less than 30°, preferably measured according to DIN 55660.2 with DIN EN 828:1997 again also being suitable, in principle.

Regarding the quantity of nanoparticles on the surface of the analytical aid, the analytical aid is preferably coated with a quantity of nanoparticles in the range from 7.5 µg per mm^2 of surface area of the analytical aid to 150 ng per mm^2 of surface area of the analytical aid.

Preferably at least 90 wt.%, more preferably at least 95 wt.%, more preferably at least 96 wt.%, more preferably at least 97 wt.%, more preferably at least 98 wt.%, more preferably at least 99 wt.%, more preferably at least 99.5 wt.%, more preferably at least 99.9 wt.%, more preferably 100 wt.%, of the hydrophilic coating consists of nanoparticles with silica structure.

In the context of the invention, the coatings can contain mixtures of different nanoparticles. Preferably the coatings contain only nanoparticles of one structure.

In the context of the invention, the surface of the analytical aid can be coated partially or completely with the hydrophilic coating. Preferably, the surface that faces the sample when using the analytical aid is coated at least partially or completely. Preferably at least 80%, more preferably at least 90%, more preferably at least 95%, more preferably at least 98%, and especially preferably at least 99% of the surface is coated.

If the analytical aid is for example a needle element, for example with at least one internal space, in particular at least one cannula and/or at least one capillary, then preferably the whole surface of the internal space of the needle element is provided with a hydrophilic coating, and especially preferably at least one capillary-active surface structure from a tip of the needle element up to an optional contact point of the needle element with at least one optional testing element, for example with at least one test chemistry for detecting at least one analyte in a body fluid.

Surface of the analytical aid

Regarding the chemical nature of the analytical aid, its surface preferably consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a metal oxide mixture. This means that the analytical aid consists per se of a metal and/or a metal alloy and/or a metal oxide and/or a metal oxide mixture or that the analytical aid is produced at least partially from another material and this material has been coated at least partially with a metal and/or a metal alloy and/or a metal oxide and/or a metal oxide mixture.

According to one embodiment, the analytical aid accordingly comprises a coating of metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

The coating of metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide can be applied in any known way, for example by sputtering,

vacuum metallization, galvanic coating or deposition from dissolved metal compounds. Moreover, several layers of metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide can also be applied.

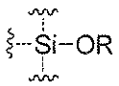
According to one embodiment of the invention, the analytical aid can, for example in the case when the analytical aid, as described below, is a testing element or distributing element, be coated by vacuum metallization, for example with aluminium. The analytical aid thus obtained is then converted for example by oxidation to a metal oxide and/or a mixed metal oxide, in particular to boehmite. The oxidation is effected for example with water, alkali-metal or alkaline-earth metal hydroxides, oxygen, hydrogen peroxide, ozone, heat in the presence of the oxygen of the air or sulphur compounds. The metallic surface is in this case at least partially oxidized, for example by the boehmite process with hot water and/or steam.

If such a coating is applied, then this coating containing metal and/or metal alloy and/or this coating containing metal oxide and/or mixed metal oxide and/or this coating containing mixed metal oxide is preferably applied on the analytical aid before step (b). Accordingly, the present invention also describes a method of production of an analytical aid, comprising a surface coated at least partially with a hydrophilic coating, and an analytical aid produced or producible by said method, wherein step (a) of the method described above comprises:

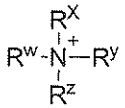
(a) providing the analytical aid, wherein provision comprises the coating of the analytical aid with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

If the analytical aid is a needle element, the analytical aid is preferably not coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

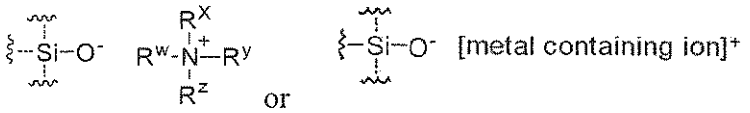
In the case when the nanoparticles comprise groups of structure (I)



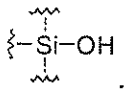
in which R is a metal-containing ion, or is



according to a preferred embodiment of the invention the nanoparticles are de-ionized before step (b). In this de-ionizing, the nanoparticles, containing the groups of structures



are converted to nanoparticles with groups of structure

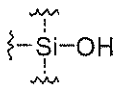


The de-ionizing can generally take place by all methods known by a person skilled in the art. Preferably the de-ionizing is effected by ion exchange chromatography or by bringing into contact with an acidic ion exchange material.

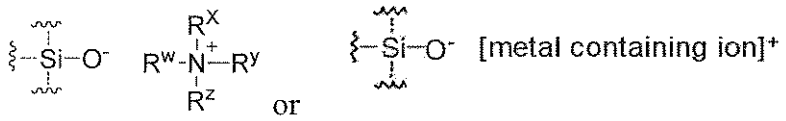
The present invention therefore relates to a method of production of an analytical aid, and an analytical aid producible by said method, comprising the following steps

(a) providing the analytical aid,

(a1) providing nanoparticles with silica structure, which have an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm, wherein the nanoparticles have groups



by de-ionizing nanoparticles with silica structure, wherein the nanoparticles have groups of structure



wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

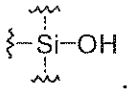
(b) coating the analytical aid by bringing the analytical aid into contact with a mixture G comprising at least one dispersant and the nanoparticles obtained according to (A1)

(c) drying the analytical aid obtained according to (b), and

(d) optionally sterilizing the analytical aid obtained according to (c),

wherein the bringing into contact in (b) preferably takes place by dip coating and/or spray coating and/or contact coating and/or at least one other of the aforementioned methods, and wherein the analytical aid and/or the surface of the analytical aid preferably consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

Accordingly, the present invention preferably also relates to an analytical aid, as described above, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure, wherein the nanoparticles contain groups of structure



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<u>Analytical aid:</u>

The term "analytical aid", as used in the context of the present invention, generally means an element, by means of which or with the aid of which at least one property of at least one sample can be determined. Basically, in this respect any analytical aids may be considered,

for example rigid analytical aids or also deformable analytical aids. The analytical aid can in particular consist completely or partially of a material selected from the group consisting of a metal, a metal oxide, a paper, a ceramic, a plastic and a textile material such as for example cellulose or synthetic fibres. Combinations of the aforementioned materials and/or other materials are also conceivable.

In particular, the analytical aid can be an analytical aid for qualitative and/or quantitative analysis of samples.

The sample can in particular be a liquid or gaseous sample. Especially preferably the sample comprises at least one body fluid or portions thereof, in particular blood or blood constituents, interstitial fluid, saliva or urine.

The at least one property can basically be any chemical, physical or biological property. Especially preferably, the at least one property comprises a concentration of at least one analyte in the sample, in particular of at least one metabolite, for example glucose, lactate or cholesterol.

Especially preferably, the analytical aid is therefore an analytical aid that can be used in the context of detecting at least one analyte in a liquid, in particular a body fluid. In particular, the analytical aid can be an analytical aid that can be used during sampling, for example when collecting a sample of a body fluid, and/or during analysis of the sample, for example in the detection of at least one analyte in a body fluid. In particular, the analytical aid can accordingly be an analytical aid or a part of an analytical aid for qualitative and/or quantitative analysis of blood and/or interstitial fluid.

Especially preferably, the analytical aid is suitable for measuring and/or for the qualitative and/or quantitative detection of at least one analyte of the body fluid, for example of the blood and/or of the interstitial fluid, for example sugar, preferably glucose, lipids, metabolic products, e.g. urea or uric acid, proteins, peptides and salts, or other constituents of the blood or of the interstitial fluid. At least one analyte to be detected can be for

example at least one metabolite, for example blood glucose, lactate, cholesterol or other metabolites.

Regarding the nature of the analytical aid, all analytical aids known by a person skilled in the art are included. Preferably the analytical aid is selected from the group consisting of a needle element, a testing element for detecting at least one analyte in a liquid, and optionally a distributing element for distributing a sample of a body fluid that has been collected.

Testing element

"Testing element" means, in the context of the present invention, all carrier-bound elements for detecting at least one analyte in a liquid. A testing element can in principle be intended for detecting at least one analyte for medical or non-medical purposes. These carrier-bound testing elements preferably comprise one or more layers, containing at least one detection reagent for detecting the at least one particular analyte of interest. Preferably these detection reagents are incorporated in corresponding layers of a carrier. Bringing the testing element and in particular the detection reagent in contact with the liquid leads, in the presence of the at least one analyte to be detected, which can also be called the target analyte, to a detectable change, for example of a physical and/or chemical nature, for example with formation of covalent, non-covalent or complex bonds between the detection reagent and the target analyte. This preferably leads to a measurable signal, for example an electrical signal and/or a colour change, preferably to a measurable optical signal, which can for example be evaluated visually or by means of equipment, for example by reflection photometry or fluorescence photometry.

Regarding the outward appearance of the testing element, all outward appearances familiar to a person skilled in the art are included in the context of the invention. In particular the testing element can be a test strip, a test tape or a test disk. Without restriction of further, alternatively or additionally usable embodiments, in particular flat, strip-shaped testing elements, i.e. test strips, are described in the following.

In addition to the at least one detection reagent, which can carry out at least one analyte-specific reaction, the testing element, in particular at least one test field of the testing element, can contain further substances, for example carriers, excipients, pigments, fillers, buffer substances or similar. In the following, no distinction will be made between further substances that also participate in the reaction for detecting the analyte, and the actual detection reagent. In particular, the detection reagent can comprise an enzymatic detection reagent. As examples of glucose-specific enzymatic detection reagents of this kind, we may mention oxidoreductase enzymes (e.g. GlucDOR/PQQ), dehydrogenase enzymes, oxidase enzymes or similar enzymes, for example glucose oxidase (GOD) or glucose dehydrogenase.

The at least one detectable reaction is, as already noted, preferably an optically detectable reaction. However, other types of reactions are basically possible. In particular, it can be a reaction in which, if the at least one target analyte is present, at least one detection substance is formed. Several detection substances can also be formed and/or used, which can be detected individually, in groups or all of them. Detection substances are thus substances that form as a result of the at least one detection reaction and/or take place in the at least one detection reaction and are detectable. Based on the at least one detection substance that is detected, for example the at least one analyte can be detected quantitatively and/or qualitatively. However, detections and/or detection substances are also possible, for which detection of the at least one detection substance is not used or is not only used for detection of the analyte, but alternatively for example for determining the volume layer of the sample thickness above the test field, as will be described below.

Preferably, the test chemistry described above for the detection of at least one target analyte with at least one detection reagent is not sensitive to the hydrophilic coating. This ensures that if traces of the hydrophilic coating become detached when using the analytical aid, the testing element can be contaminated without affecting the test chemistry. Therefore, owing to the insensitivity of the test chemistry to the coating, the test for detection of the target analyte is not, or is only insignificantly, falsified by traces of the compound of formula (I) or degradation products thereof. Preferably, during use for

determination, essentially no, more preferably no, proportion of the hydrophilic coating becomes detached from the analytical aid.

Regarding the structure of the testing element, this has preferably at least one carrier element, in particular a carrier strip. This carrier element can comprise for example a plastic material, a ceramic material, a paper material, a composite material or similar. The test field can then be applied on this carrier element. The carrier element can be used for providing a mechanically supporting function for the testing element, for example to enable the testing element to be held during sample application and/or during a measurement. The at least one hydrophilic coating can for example be applied completely or partially on the carrier element and/or in particular on the test chemistry and/or on one or more other elements of the testing element.

The carrier element can for example comprise at least one film element, in particular at least one plastic film. The film element preferably has a closed surface, which preferably is essentially impermeable to the sample. Preferably the film element is of non-porous design, has a non-porous surface or has pores with an average pore radius of not more than 5 μm, preferably of not more than 1 μm. Therefore the film element differs for example from conventional network-like materials, for example spreading networks. Generally the carrier element and/or the carrier surface can have at least one material that is essentially impermeable to the sample.

Distributing element

A distributing element is to be understood, in the context of the invention, as a device with which a sample received, in particular a liquid sample, can be distributed over a two-dimensional distribution region and/or a three-dimensional distribution volume. In particular, for uniform, extensive and rapid distribution of the sample to be analysed, preferably small blood samples, the distributing element can preferably be arranged on testing elements, for example test strips, in particular glucose test strips.

The distributing element can in particular be selected from the group consisting of a capillary structure, a membrane, a network, in particular a spreading network. Preferably, in the context of the invention, the distributing element is a spreading network. A membrane is to be understood, in the context of the present invention, as a porous element, for example a porous film or porous layer, which is arranged in order to take up the sample and distribute it preferably laterally, i.e. parallel to a plane of the film or layer. In particular the membrane can comprise at least one porous plastic film. The term "spreading network" is to be understood, in the context of the present invention, expressly as a generic term for all filament structures suitable for purposes of spreading or distribution or transfer. This includes, among others, textiles, knitted fabrics and fleeces. The term "filament" comprises both mono- and poly-filaments of uniform or non-uniform material basis and dimensioning. It should be mentioned that sample transfer preferably takes place through the filament structure.

According to a preferred embodiment, the membrane and/or the spreading network lie on at least one layer of a testing element, for example a detection layer of the testing element, containing the at least one detection reagent, and/or a separating layer, containing at least one reflecting pigment and/or at least one substance that is arranged for separating sample constituents, for example red blood cells. The sample liquid applied can thus be led for example by the spreading network envisaged according to the invention, by capillary action to the layer containing the at least one detection reagent and, at the points of contact of the spreading network and detection layer, can be spread or distributed, also by capillary forces, on the detection layer. The spreading network therefore serves preferably as an aid for undirected (isotropic) two-dimensional distribution of a liquid sample at the target location, namely on the at least one layer containing the at least one detection reagent. The desired intermediate storage and superficial spreading of the sample only occur in interaction with the spreading network, with the spreading network demarcating, with respect to the detection layer, a large number of varying capillary-active interstices or capillary gaps, which owing to the surface contour of the filaments and the spatial arrangement thereof, are largely undirected overall.

As described above, the surface of the analytical aid preferably comprises a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide. Accordingly, the analytical aid, according to a preferred embodiment, is a distributing element comprising a surface consisting of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide. Preferably, in the context of the invention, the analytical aid is a distributing element, for example a spreading network, which can be coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide, as described above.

Accordingly, the present invention also relates to an analytical aid, wherein the analytical aid is a spreading network, optionally coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide.

Needle element

According to an alternative preferred embodiment, the analytical aid is a needle element or comprises said needle element. In this case, a needle element can basically be any element with a tip or blade, which is arranged for producing an opening in a portion of a user's skin. For example, a lancet, a cannula, in particular a hollow cannula, an at least partially open hollow cannula, a microcutter or the like, a capillary, in particular a capillary gap, can be used as the needle element.

If the needle element is a lancet, the lancet can in particular comprise a so-called microsampler, i.e. an element that has both a tip and/or blade for producing a puncture and at least one capillary channel for taking up the sample. Furthermore, the microsampler can optionally have at least one testing element for detecting at least one analyte in the sample.

In general, the needle element can have at least one capillary-active surface structure, which is also simply called capillary structure in the following and which need not necessarily be arranged completely on a surface of the needle element. In particular the capillary structure can have at least one capillary channel and/or at least one capillary trough. Owing to the capillary action of the surface structure, the body fluid flowing from the puncture site can be taken up by the capillary structure and for example be transported

to a testing element arranged on the needle element. The capillary structure can provide a receiving volume, for example for receiving an amount of body fluid required for one or more tests. Said surface structure can be formed by at least one capillary trough running parallel and/or at least partially transversely to the longitudinal axis of the needle element. In the case of capillary troughs running parallel to the longitudinal axis of the needle element, a number of said capillary troughs from 2 to 6, in particular 2 or 3, is preferred. However, it is also possible, for example, for up to 10 capillary troughs to be formed on the needle element. In the case for example of a hollow cannula, the capillary structure is formed by the hollow shape of the cannula.

In particular the possibility of targeted uptake and/or targeted transport of body fluid out of or from the puncture site is advantageous in the design of said capillary structures. For example, transport can take place to at least one testing element, for example to at least one testing element arranged on or arrangeable on the needle element or to the needle element. The testing element can be arranged fixed to the needle element and/or the capillary structure, but it can also be mounted movably to these, for example so that after uptake of the body fluid into the capillary structure, the testing element is moved towards the capillary structure. Advantageously, the hydrophilic coating and/or a plasma treatment and/or formation of nano- and microstructures at least in the capillary troughs, but also on the whole surface, additionally contribute to the capillary action.

Hydrophilic coating of the needle element can be complete or also partial. Preferably the whole surface of the needle element is provided with a hydrophilic coating, and especially preferably the at least one capillary-active surface structure from the tip of the needle element to the needle element/testing element contact point.

If for example a body fluid is taken up with the needle element, the body fluid is preferably transported along the needle element within 30-1000 ms per millimetre of transport distance from the puncture site to the testing element, especially preferably within 40-700 ms/mm of transport distance and quite especially preferably within 40-400 ms/mm of transport distance. The term transport distance means the distance that is travelled, preferably can be travelled as a maximum, in the needle element by the sample that is

taken up. The total transport distance can for example have a length from 0.5 mm to 10 mm, in particular 1 mm to 5 mm. For example, the transport distance can be a total length of a capillary, for example a capillary gap, in the needle element. Alternatively or additionally, the term transport distance can also refer to the length of the needle element from a tip to a discharge opening, for example in the case of a cannula. At least one testing element with at least one test chemistry for detecting the analyte can be provided, which can be completely or partially a constituent of the needle element, but which can also be formed completely or partially separately from the needle element. If the testing element is not a constituent of the needle element, transfer of the body fluid from the needle element can also take place with a time delay after uptake of the body fluid by the needle element. Until this transfer, for example a further period of time can elapse, for example a period from 0.5 s to 5 s after commencement of puncture and/or after retraction of the needle element from the body tissue, in particular a period from 1 s to 2 s.

Preferably the analytical aid is a needle element of a sampling device for collecting a body fluid.

Accordingly, the present invention also relates to an analytical aid, as described above, wherein the analytical aid is a needle element of a sampling device for collecting a body fluid. The present invention further relates to a method of production of an analytical aid, as described above, and an analytical aid, producible or produced by this method, wherein the analytical aid is a needle element of a sampling device for collecting a body fluid.

The present invention further relates to a sampling device for collecting a body fluid. A sampling device is generally to be understood as a device that is arranged for taking up a sample for the purpose of an analysis. Preferably, moreover, the sampling device is also arranged for generating the sample, for example by making a puncture and/or cut in a skin surface, for example using at least one needle element. Alternatively or additionally, the sampling device can also be arranged for detecting at least one analyte in the sample, for example by means of at least one testing element, for example according to one or more of the embodiments described above.

The sampling device comprises at least one analytical aid with at least one surface coated at least partially with a hydrophilic coating, according to one or more of the embodiments described above, with the proviso that the analytical aid is selected from the group consisting of a needle element and a testing element. With respect to the possible embodiments of the needle element and/or of the testing element, reference may be made to the above description and to the embodiments described hereunder. The needle element can in particular comprise at least one microsampler, which is provided completely or partially with the at least one coating, in particular in the region of a capillary structure. The testing element can in particular comprise at least one distributing element provided with the hydrophilic coating, preferably at least one spreading network provided with the hydrophilic coating, which can for example be located on at least one test field of the testing element.

The sampling device can thus, as described above, have at least one needle element for taking a sample of a body fluid and/or at least one testing element, with which at least one analyte in the respective body fluid can be detected qualitatively and/or quantitatively. The testing element can in particular be connected to the needle element, so that the body fluid can travel from the needle element to the testing element, for example a sample application point or a sample application surface of the testing element. Alternatively or additionally, however, the testing element can also be arranged as a separate testing element or can be applied in some other way in or on the sampling device, for example in at least one chamber, in which for example the needle element can also be located. A transfer mechanism can be provided, which transfers the body fluid taken up by the needle element to the testing element. This can take place for example in that, by means of an actuator or some other mechanism, the needle element with the body fluid is brought closer to the testing element, so that the body fluid is transferred at least partially from the needle element to the testing element, for example a test field of the testing element. For example, for this purpose the needle element and/or at least one capillary structure of the needle element can be placed on the test field. However, other embodiments are also possible. So that the body fluid can pass from the capillary-active surface structure into the testing element, the testing element is preferably to be constructed, at a connecting point between testing element and surface structure, so that the body fluid is transferred by suction from

the surface structure into the testing element. For this, it is desirable for the testing element to be provided with a capillary-active component, e.g. an absorbent fleece or a fibre bundle, whose capillary action is greater than the capillarity of the surface structure. Alternatively or additionally, however, it can also simply be designed so that the capillary is brought into contact with the chemistry, for example by placing the capillary on the chemistry, optionally also with application of pressure. Moreover, contact should be ensured between the surface structure of the cannula and the capillary-active component of the testing element.

Moreover, the sampling device can have at least one sensor. This sensor can for example be of electrochemical and/or optical design. In the case of an electrochemical sensor, through catalytic action of the test chemistry, a substance of the body fluid that is to be determined can be reacted and this reaction can be measured electrochemically, whereas in the case of an optical sensor, a product of reaction of the test chemistry with a substance contained in the body fluid is irradiated with light of a defined wavelength and for example a degree of absorption of this light and/or a degree of reflection of the light and/or the fluorescence of the sample are measured.

Furthermore, the sampling device can be equipped with a conducting element, in particular an electrical conducting element. In the case of an electrochemical sensor, this conducting element can be a metal layer applied on a plastic film, and/or a metal foil or a metal wire, which is optionally injected into the respective component, e.g. by an injection moulding process. The conducting element can also be formed from conductive plastic or in some other way, for example by means of conductive ink. The sampling device can also have at least one electrical and/or optical contact point, via which the sampling device can be coupled to peripheral equipment. Thus, the sampling device can be supplied with current via an electrical contact point and information can be transferred via said electrical contact point. Light can be transferred between peripheral equipment and the sampling device via an optical contact point. In the case of an optical sensor, said sampling device can be equipped both with an electrical and with an optical contact point.

Preferably, the sampling device can be designed completely or partially as a disposable article and/or a multi-use article, wherein in the case of a disposable article, the sampling device is disposed of after a single use, whereas in the case of a multi-use article, multiple use is intended. Magazining of one or more sampling devices and/or of parts thereof is also conceivable, similar for example to the magazining of lancets in lancing aids, for example by storing several sampling devices as a whole in a magazine and/or wherein a sampling device contains for example several testing elements and/or several needle elements in magazined form.

As described above, the analytical aid, preferably the needle element and/or the testing element, can be produced at least partially from a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide. Moreover, the material of the needle element and/or of the testing element should be inert, in particular with respect to the body fluid to be sampled, and biocompatible, and mechanically strong as well as easy to sterilize. Preferably, the needle element can be made of surgical steel, wherein said surgical steel can be provided with a coating of metal oxides. Alternatively or additionally to a metallic material, the needle element can, however, completely or partially, also be produced in another material or comprise another material, for example a plastic material and/or a ceramic material. In particular, embodiments are also included within the scope of the invention, in which the needle element per se, as described above, is coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide, and the hydrophilic coating is applied on this surface, for example a surface of this coating.

The analytical aid according to the invention and the methods according to the invention have a multiplicity of advantages over known analytical aids and methods. Thus, we surprisingly found the hydrophilic coating with nanoparticles of the kind described above firstly to result in surface properties with excellent hydrophilicity. Secondly, the coating surprisingly is distinguished by good long-term stability, thereby making it possible to ensure stable storage over a relatively long period of time. More specifically, the hydrophilic properties of the coating can be shown to be impaired only marginally, if at all, even by direct or indirect contact with various materials of the analytical aid, such as

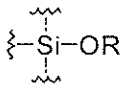
plastic materials, adhesives or metals for example. In addition, strain due to sterilization, for example radiation strain caused by β rays and/or γ rays and/or strain due to chemical disinfectants such as ethylene oxide, for example, also do not or only marginally impair the hydrophilic properties of the coating. As a result, a long-term stability of 6-12 months or more can be achieved without problem, while the hydrophilic surface properties are maintained.

Moreover, the coating used according to the invention, is extremely resistant to contaminations and itself does not contaminate a collected sample, for example. Accordingly, the analytical aid may optionally also be used multiple times. More specifically, a coating employed according to the invention may be employed in capillary elements and/or channels of the analytical aid, with these elements having long-lasting hydrophilicity due to the coating according to the invention.

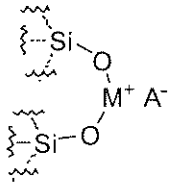
Moreover, the coating used according to the invention can be prepared in a simple and reliable manner, for example by using the method of the invention according to one or more of the developments described above or the embodiments to be described in more detail below. More specifically, the surface coating can be applied, for example, from an aqueous solution and/or an aqueous dispersion. An application method of this kind can easily be carried out.

The following embodiments are especially preferred in the context of the invention:

1. Analytical aid, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm and the nanoparticles comprise groups of structure (I) and/or (II)

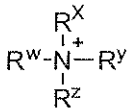


(I)

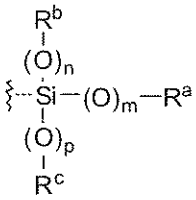


(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



and



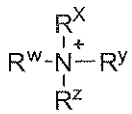
and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

2. Analytical aid according to embodiment 1, wherein R is selected from the group consisting of H, an alkaline-earth metal ion, an alkali metal ion,



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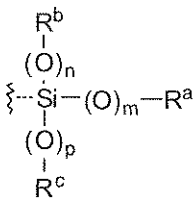
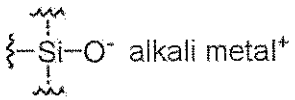


and wherein $M^+ = Al^+$.

3. Analytical aid according to embodiment 1 or 2, wherein the hydrophilic coating comprises nanoparticles with silica structure, which comprise groups of structure (I), and wherein R = H.

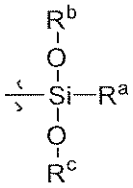
4. Analytical aid according to embodiment 1 or 2, wherein the hydrophilic coating comprises nanoparticles with silica structure, which comprise groups of structure



wherein alkali metal$^+$ is preferably a sodium ion or a potassium ion, and quite especially preferably is Na^+.

5. Analytical aid according to embodiment 1 or 2, wherein the hydrophilic coating contains nanoparticles with silica structure, which have groups of structure (I), with $R = NH_4^+$.

6. Analytical aid according to embodiment 1 or 2, wherein the hydrophilic coating contains nanoparticles with silica structure, which have groups of structure (I), wherein R has the following structure



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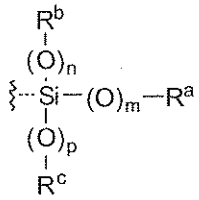
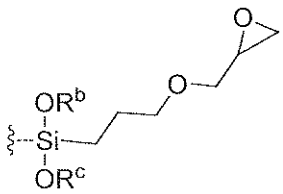
7. Analytical aid according to one of the embodiments 1 to 6, wherein the silica structure of the nanoparticles has at least one foreign atom, selected from the group consisting of Sn, Ti, Zr, Hf, Ge, In, Ga, P, Al or B, preferably wherein the foreign atom is Al.

8. Analytical aid according to one of the embodiments 1 to 7, wherein the nanoparticles have an average particle size in the range from 1 to 100 nm, more preferably in the range from 1 to 50 nm, more preferably in the range from 3 nm to 25 nm, and especially preferably in the range from 5 to 15 nm.

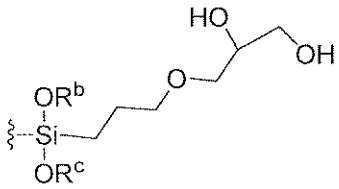
9. Analytical aid according to one of the embodiments 1 to 8, wherein 10 to 40% of all groups R are



10. Analytical aid according to one of the embodiments 1 to 9, wherein the group of formula (I) has a structure of formula (Ia) or (Ib):



(Ia)



(Ib)

wherein R^b and R^c, independently of one another, are selected from the group consisting of H and alkyl.

11. Analytical aid according to one of the embodiments 1 to 10, wherein the hydrophilic coating consists of the nanoparticles with silica structure.

12. Analytical aid according to one of the embodiments 1 to 11, wherein the surface of the analytical aid coated at least partially with the hydrophilic coating consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide.

13. Analytical aid according to one of the embodiments 1 to 12, wherein the nanoparticles have an average particle size in the range from 1 to 100 nm and wherein the hydrophilic coating has a thickness, in particular on average a thickness, in the region of max. 500 nm, preferably of max. 300 nm and especially of max. 100 nm.

14. Analytical aid according to one of the embodiments 1 to 14, wherein the surface of the hydrophilic coating has a contact angle with water of less than 60°, preferably measured according to DIN 55660.2.

15. Analytical aid according to one of the embodiments 1 to 15, wherein the analytical aid is selected from the group consisting of a needle element, in particular a lancet, a capillary, in particular a capillary gap, a cannula, a testing element for detecting at least one analyte in a body fluid and a distributing element for distributing a sample of a body fluid that has been collected, in particular a spreading network, optionally coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide, or a plastic film, optionally coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide.

16. Analytical aid according to one of the embodiments 1 to 16, wherein the analytical aid is a needle element (112) of a sampling device (110) for taking a sample of body fluid.

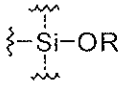
17. Method of production of an analytical aid, comprising a surface that is coated at least partially with a hydrophilic coating, wherein the method comprises:

(a) providing the analytical aid,

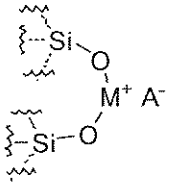
(b) coating the analytical aid by bringing the analytical aid into contact with a mixture G comprising at least one dispersant and nanoparticles with silica

structure, which have an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm,

wherein the nanoparticles comprise groups of structure (I) and/or (II)

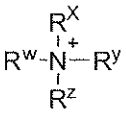


(I)



(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



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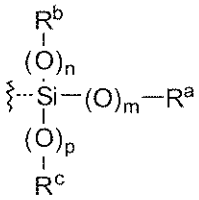


and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion,

(c) drying the analytical aid obtained according to (b), and

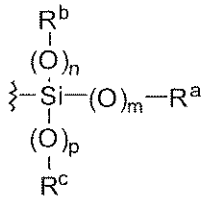
(d) optionally sterilizing the analytical aid obtained according to (c),

wherein the bringing into contact in (b) preferably takes place by dip coating and/or spray coating and/or contact coating, and wherein the analytical aid and/or the surface of the analytical aid preferably consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

18. Method according to embodiment 17, wherein the surface of the analytical aid to be coated is treated before step (b) with at least one etchant and/or with plasma or corona.

19. Method according to embodiment 17 or 18, wherein the at least one dispersant is water and wherein mixture G preferably has a pH in the range from 2 to 10.

20. Method according to one of the embodiments 17 to 19, wherein the nanoparticles comprise groups of structure (I), and wherein 10 to 40% of all groups R are

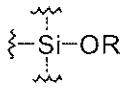


21. Analytical aid, producible or produced by a method according to one of the embodiments 17 to 20.

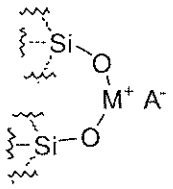
22. Analytical aid according to embodiment 21, wherein the analytical aid is a needle element of a sampling device for collecting a body fluid.

23. Sampling device (110) for taking a sample of body fluid, containing at least one analytical aid according to one of the preceding embodiments relevant to an analytical aid, with the proviso that the analytical aid is selected from the group consisting of a needle element (112) and a testing element.

24. Use of nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm as hydrophilic coating (122) for a surface of an analytical aid, preferably as hydrophilic coating (122) for a needle element (112) of a sampling device (110) for taking a sample of body fluid, wherein the nanoparticles comprise groups of structure (I) and/or (II)

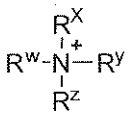


(I)

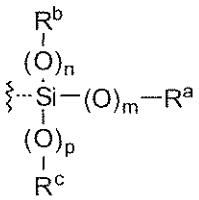


(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



and



and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

Brief description of the drawings

Further details and features of the invention can be seen from the following description of preferred examples, in particular in conjunction with the subclaims. The respective features can be realized just in themselves or several in combination with one another. The invention is not limited to the examples.

Fig. 1 shows an example of a sampling device.

Examples

Fig. 1 is a highly schematic sectional side view of an example of a possible sampling device 110 according to the invention. The invention can, however, also be applied to a large number of other types of sampling devices and analytical aids.

The sampling device 110 comprises a needle element 112, shown schematically in Fig. 1, with a tip 114, which on movement of the needle element 112 in a puncturing direction 116 pierces a portion of a user's skin. The movement of the needle element 112 can for example be driven by an optional actuator 118 of the sampling device 110, which is shown schematically in Fig. 1 and which can be arranged in various ways known by a person skilled in the art. The actuator 118 can bring about a forward movement of the needle element 112 in the puncturing direction 116 and optionally also a backward movement of the needle element 112 against the puncturing direction.

The needle element 112 can, in the example shown or also in other examples, in addition optionally comprise at least one capillary-active surface structure in the form of for example a capillary structure 120, for example at least one capillary gap, which can in

particular extend parallel to the puncturing direction 116. Other embodiments of the capillary structure 120 are also possible. The capillary structure 120 can for example serve for taking up and/or for transporting a sample of the body fluid in a sampling operation, when the needle element 112 penetrates into a body tissue. For example, transporting or taking-up of the sample can take place by capillary forces.

The needle element 112 further comprises at least one hydrophilic coating 122, preferably in the region of the capillary structure 120. Possible embodiments of this hydrophilic coating 122 and possible methods and examples of production thereof are explained in more detail below.

The sampling device 110 can further comprise at least one testing element 124, for example with at least one test chemistry, for detecting at least one analyte in the body fluid. For example, this testing element comprises at least one test field, thus at least one area coated with the test chemistry. In Fig. 1, the testing element 124 is shown symbolically as testing element 124, formed separately from the needle element 112, and which can be arranged for example in or on a housing 126 of the sampling device 110, for example a magazine housing. For example, after a sample is taken up, the needle element 112 with the capillary structure 120 can be brought closer to the testing element 124, in order to transfer a sample of the body fluid or a portion thereof from the capillary structure 120 to the testing element 124. For this purpose, for example in the sampling device 110, an actuator 128 can be provided, which moves the needle element 112 or a part thereof, after sample uptake, in a direction of movement 130 towards the testing element 124. Alternatively or additionally, however, there are also other possibilities for transferring the body fluid from the capillary structure 120 and/or from the needle element 112 to the testing element 124, for example by passing the needle element 112, during a backward movement after sample collection, along a suitable path past the testing element 124. Once again, however, it is also possible, alternatively or additionally, to integrate the optional testing element completely or partially in the needle element 112, for example at one end of the capillary structure 120.

Various examples relating to the production of hydrophilically coated analytical aids are explained below.

Examples:

Example 1: Coating of the capillaries and verification of the shelf lives of hydrophilizing agents

Materials used:

- capillaries with cross-sections of 120x80 μm
- Makrolon® 2458 (Bayer) granules coating materials:
  1. Ar plasma
  2. Heparin
  3. Carbopol® 971PNF (Na salt of a partially crosslinked high-molecular polyacrylic acid) (commercially available for example from Lubrizol)
  4. Mega 8 (octanoyl-N-methylglucamide) (commercially available for example from Dojindo)
  5. DONS (dioctylsodium succinate) (commercially available for example from Cytec Industries B.V.)
  6. PVA 28-99 (polyvinyl alcohol) (commercially available for example from Fluka)
  7. PVP K15 (polyvinyl pyrrolidone) (commercially available for example from Aldrich)
  8. Bindzil® CC30 (nano-silica dispersion) (Akzo Nobel)
  9. Ludox® AM-30 (nano-silica dispersion) (commercially available for example from Aldrich)
  10. Ludox® AS-30 (nano-silica dispersion) (commercially available for example from Aldrich)
  11. Bindzil® 2034DI (nano-silica dispersion) (commercially available for example from Akzo Nobel or EKA)
  12. CMC (carboxymethyl cellulose, MW = 700 000 g/mol, degree of substitution DS 0.9) (commercially available for example from Aldrich)
  13. Bindzil® CC301 (nano-silica dispersion) (Akzo Nobel)

14. Bindzil® CC401 (nano-silica dispersion) (Akzo Nobel)
15. Bindzil® 33/360 (nano-silica dispersion) (Akzo Nobel)

General specification 1(a) for coating capillaries

Coating is effected by allowing the aqueous dispersions or solutions of the coating materials to flow purely by capillary forces into the capillaries with cross-sections of 120x80 µm, until the capillaries are completely filled (approx. 35 nanolitres). Then the coating is dried briefly with an air blower at room temperature or by heating to 140°C.

Prior to coating, the capillaries are made wettable by a plasma treatment.

General specification 1(b) for plasma treatment of the capillaries

The capillaries are treated for 30 s in a plasma stove (manufacturer: Plateg) at 50 mbar argon pressure and 400 W microwave power.

General specification 1(c) for sterilization

Sterilization is effected by treatment with beta radiation, 25 kGy.

Example 1.1 Shelf lives of hydrophilizing agents in the presence of Makrolon

The shelf lives of the various hydrophilizing agents in the presence of volatile constituents of packaging materials were verified for the example of Makrolon® as such a material, by in each case heat-sealing 6 capillaries coated according to general specification 1(a), which were treated with plasma prior to coating according to general specification 1(b), with in each case 4 g of granules of Makrolon 2458 or without granules, in a PET bag and storing them for the specified time. Unless stated otherwise, all bags were sterilized with 25kGy beta radiation. The time for filling on a length of 4 mm was measured. The measurement was carried out with heparin-blood, HK 44. The results are presented in Table 1.

Table 1

Material	Concentration of the solution/ dispersion used [in water] (w/w)	directly after sterilization	sterilized 8 days / 75°C without Makrolon	sterilized 8 days / 75°C with Makrolon	sterilized 21 days / 75°C with Makrolon
Ar-plasma*	--	< 300 ms (without sterilization)	does not fill	does not fill	--
Heparin*	0.05%	--	300 ms	does not fill	--
Carbopol® 971PNF*	0.1%	--	450 ms	625 ms	approx. 2100 ms
Mega 8*	0.05%	does not fill	does not fill	does not fill	--
DONS*	0.05%	does not fill	does not fill	does not fill	--
PVA 28-99*	0.05%	approx. 2000 ms	> 2500 ms	approx. 2000 ms	--
PVP K15*	0.05%	--	545 ms	680 ms	--
Bindzil® CC30	0.5%	--	225 ms	200 ms	210 ms
Ludox® AM-30	0.5%	--	342 ms	400 ms	320 ms
Ludox® AS-30	0.5%	--	270 ms	240 ms	260 ms
Bindzil® 2034DI	0.5%	--	305 ms	240 ms	300 ms

* not according to the invention

The results provide evidence that the coatings according to the invention, even after storage in PET bags in the presence of Makrolon, permit a filling time of less than 400 ms for 4 mm length at a cross-section of 120x80 µm.

Example 1.2 Shelf lives of hydrophilizing agents in the presence of Zylar

The shelf lives of the various hydrophilizing agents in the presence of volatile constituents of packaging materials were also verified for the example of Zylar®, which contains a higher proportion of volatile substances compared with Makrolon, by storing in each case 6 capillaries coated according to general specification 1(a), which were treated with plasma prior to coating according to general specification 1(b), together with injection mouldings in the material Zylar 220 (MBS copolymer, manufacturer: Ineos-Nova, approx. 1.5 mm thick, weight 4 g). The time for filling on a length of 4 mm was measured. Measurement was carried out with heparin-blood, HK 44. The results are presented in Table 2.

Table 2

Material	Concentration silica in water w/w	Directly after sterilization, with Zylar 220	1 week 75°C with Zylar 220	2 weeks 75°C with Zylar 220
Bindzil® CC301	0.5%	<300	<500	<700
Bindzil® CC30	0.5%	<300	<500	<700
Bindzil® CC401	0.5%	<300	<500	<700
Ludox® AS-30	0.5%	<300	No filling	No filling
Ludox® AM-30	0.5%	<300	No filling	No filling
Bindzil® 30/360	0.5%	<300	No filling	No filling

In the presence of Zylar, the coatings with silica nanoparticles modified by organic groups display advantages over the silica nanoparticles with no organic modifications.

Example 1.3: Comparative example: Shelf lives of hydrophilizing agents in the presence of Zylar with non-inventive coating:

By way of a comparative example for comparing coatings according to the invention with non-inventive coatings, the exemplary embodiment described in Example 1.2 was repeated once more with non-inventive coatings. The coating material applied here comprised mixtures of carboxymethyl cellulose with DONS, that is coatings which are described in EP 2 014 727 A1. The coating involved firstly preparing an aqueous solution of said carboxymethyl cellulose, to which the appropriate amount of DONS was added. The aqueous solution obtained was used for coating according to general specification 1(a).

The shelf lives of the particular mixtures of CMC and DONS in the presence of volatile constituents of packaging materials were again determined for the example of Zylar, according to Example 1.2.

The results are presented in Table 3.

Table 3

Material (mass ratio)	Concentration in water w/w	Directly after sterilization, with Zylar 220	1 week 75°C with Zylar 220
CMC/DONS (20:1)	0.05 %	<300	No filling
CMC/DONS (10:1)	0.05 %	<300	No filling

In the presence of Zylar, the capillaries having the coatings with CMC and DONS did not fill anymore even after one week.

Reference numbers

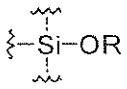
110	sampling device
112	needle element
114	tip
116	puncturing direction
118	actuator
120	capillary structure
122	hydrophilic coating
124	testing element
126	housing
128	actuator
130	direction of movement

Roche Diagnostics GmbH
F. Hoffmann-La Roche AG

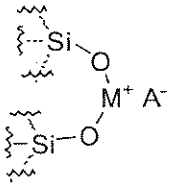
24 February 2012
RD26962PC ST/RZ/sj

Patent claims

1. Analytical aid, comprising a surface coated at least partially with a hydrophilic coating, wherein the hydrophilic coating contains nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm and the nanoparticles comprise groups of structure (I) or (II)

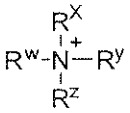


(I)



(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



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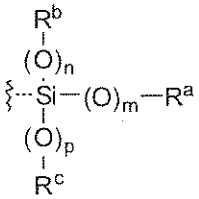


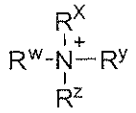
and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.

2. Analytical aid according to Claim 1, wherein R is selected from the group consisting of H, an alkaline-earth metal ion, an alkali metal ion,



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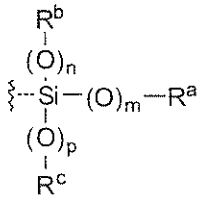
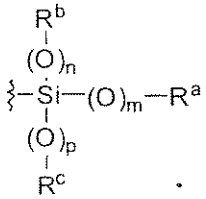


and wherein $M^+ = Al^+$.

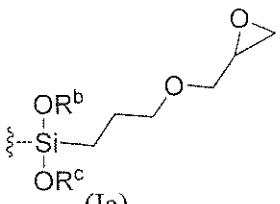
3. Analytical aid according to Claim 1 or 2, wherein the silica structure of the nanoparticles has at least one foreign atom, selected from the group consisting of Sn, Ti, Zr, Ge, In, Ga, Al and B, preferably wherein the foreign atom is Al.

4. Analytical aid according to one of Claims 1 to 3, wherein the nanoparticles have an average particle size in the range from 1 to 100 nm, preferably in the range from 1 to 50 nm, more preferably in the range from 3 nm to 20 nm.

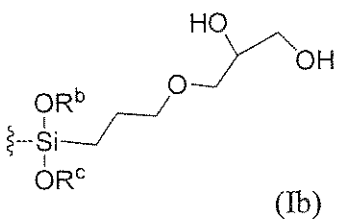
5. Analytical aid according to one of Claims 1 to 4, wherein 10 to 40% of all groups R are



6. Analytical aid according to Claim 4, wherein the group of formula (I) has a structure of formula (Ia) or (Ib):



(Ia)



(Ib)

wherein R^b and R^c, independently of one another, are selected from the group consisting of H and alkyl.

7. Analytical aid according to one of Claims 1 to 5, wherein the hydrophilic coating consists of the nanoparticles with silica structure.

8. Analytical aid according to one of Claims 1 to 7, wherein the surface of the analytical aid, coated at least partially with the hydrophilic coating, consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide.

9. Analytical aid according to one of Claims 1 to 7, wherein the nanoparticles have an average particle size in the range from 1 to 100 nm and wherein the hydrophilic coating has a thickness, in particular an average thickness, in the region of max. 500 nm, preferably of max. 300 nm and especially of max. 100 nm.

10. Analytical aid according to one of Claims 1 to 9, wherein the surface of the hydrophilic coating has a contact angle with water of less than 50°, preferably measured according to DIN 55660.2.

11. Analytical aid according to one of Claims 1 to 10, wherein the analytical aid is selected from the group consisting of a needle element, in particular a lancet, a capillary, in particular a capillary gap, a cannula, a testing element for detecting at least one analyte in a body fluid and a distributing element for distributing a sample of a body fluid that has been collected, in particular a spreading network, optionally coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide, or a plastic film, optionally coated with a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide.

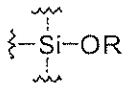
12. Analytical aid according to one of Claims 1 to 11, wherein the analytical aid is a needle element of a sampling device for taking a sample of body fluid.

13. Method of production of an analytical aid, comprising a surface that is coated at least partially with a hydrophilic coating, wherein the method comprises:

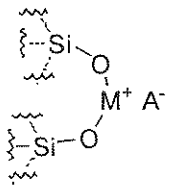
(a) providing the analytical aid,

(b) coating the analytical aid by bringing the analytical aid into contact with a mixture G comprising at least one dispersant and nanoparticles with silica structure, which have an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm,

wherein the nanoparticles comprise groups of structure (I) or (II)

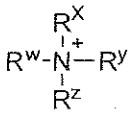


(I)

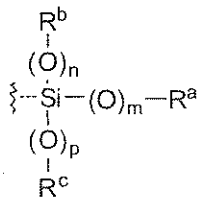


(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



and



and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion,

(c) drying the analytical aid obtained according to (b), and

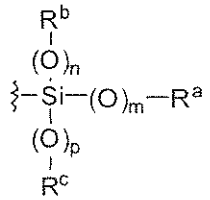
(d) optionally sterilizing the analytical aid obtained according to (c),

wherein the bringing into contact in (b) preferably takes place by dip coating and/or spray coating and/or contact coating, and wherein the analytical aid and/or the surface of the analytical aid preferably consists at least partially of a metal and/or a metal alloy and/or a metal oxide and/or a mixed metal oxide and/or a mixed metal oxide.

14. Method according to Claim 13, wherein the surface of the analytical aid to be coated is treated before step (b) with at least one etchant and/or with plasma.

15. Method according to Claim 13 or 14, wherein the at least one dispersant is water and wherein mixture G preferably has a pH in the range from 2 to 10.

16. Method according to one of Claims 13 to 15, wherein the nanoparticles comprise groups of structure (I), and wherein 10 to 40% of all groups R are

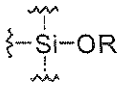


17. Analytical aid, producible or produced by a method according to one of Claims 13 to 16.

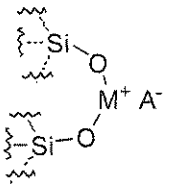
18. Analytical aid according to Claim 17, wherein the analytical aid is a needle element of a sampling device for collecting a body fluid.

19. Sampling device for taking a sample of body fluid, containing at least one analytical aid according to one of the preceding claims referring to an analytical aid, with the proviso that the analytical aid is selected from the group consisting of a needle element and a testing element.

20. Use of nanoparticles with silica structure and an average particle size, determined according to DIN ISO 22412:2008, in the range from 1 to 500 nm as hydrophilic coating for a surface of an analytical aid, more preferably as hydrophilic coating for a needle element of a sampling device for taking a sample of body fluid, wherein the nanoparticles comprise groups of structure (I) or (II)

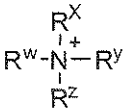


(I)

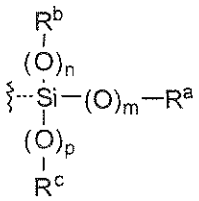


(II)

wherein in each of the groups of structure (I), independently of one another, R is selected from the group consisting of H, a metal-containing ion,



and



and wherein R^w, R^x, R^y and R^z, independently of one another, are selected from H and alkyl,

and wherein R^a, R^b and R^c, independently of one another, are optionally substituted residues, selected from the group consisting of H, alkyl, aryl, heteroaryl, cycloalkyl, cycloheteroalkyl, alkenyl and alkoxyalkyl,

and wherein n, m and p, independently of one another, are 0 or 1,

and wherein M^+ is a metal ion and A^- is a physiologically compatible anion.