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(54) **ASSAY COMPONENTS FOR DIAGNOSTIC IN VITRO APPLICATIONS .**

(57) The invention relates to a receptacle and method for in vitro diagnostic applications. The present invention facilitates in vitro diagnostic applications and minimizes the number of potential error sources by providing a receptacle with an immobilized assay component that can be re-suspended.

ASSAY COMPONENTS FOR DIAGNOSTIC IN VITRO APPLICATIONS

DESCRIPTION

Field of the invention

[0001] The field of the invention relates to a receptacle and method for in vitro diagnostic applications.

Background of the invention

[0002] A variety of in vitro diagnostic assays are routinely carried out in clinical diagnostics and life sciences.

[0003] In many in vitro diagnostic applications, so called beads are added to the reaction in a reaction vessel. These beads are usually in suspension in an aqueous buffer. During transportation, the beads possibly splash onto the vessel wall for example and then dry there. Therefore, the beads must be re-suspended in their transport vessel before they are added to the reaction vessel by pipetting and used for the reaction.

[0004] In standard in vitro diagnostic applications, the reactants can be placed in a previously empty reaction vessel for the detection of analytes. The reactants are mostly in liquid solutions and individually and successively transferred from separate transport vessels into the actual reaction vessel using pipetting needles.

[0005] Some reactants, such as beads for example, do not form a uniform suspension and need to be brought into homogenous suspension inside their transport vessel prior to pipetting. Beads for example tend to sink down inside their solution and collect at the bottom of the vessel, or they splash onto the vessel wall or the lid. The beads need then to be washed down and brought back into suspension by swiveling, agitation, shaking, stirring, pipetting or alternating magnetic fields.

[0006] There are several disadvantages in the prior art. Reactants need to be pipetted separately into the vessel and thereby be distributed homogenously. Homogeneous distribution of beads for instance, is of central importance in quantitative analyzes. Reactants

need to be brought into a homogeneous suspension before being pipetted into the reaction vessel in order to avoid measurement errors, because reactants can set down for example. Otherwise, an inhomogeneous bead distribution can lead to an incorrect bead concentration in the reaction vessel and thus to measurement errors.

[0007] In open transport vessels, the concentration of reactants such as beads, may change as a result of evaporation. At a constant pipetting volume, pipetting of the reactants into the reaction vessel then results in an increased concentration of beads in the reaction vessel. This results in measurement errors. Furthermore, the bead concentration in the transport vessel changes as a result of the transfer of liquid, for example washing liquid, from the pipetting needle to the vessel. Pipetting into the reaction vessel with the same pipetting volume thus results in a reduced bead concentration in the reaction vessel and results in measurement errors.

[0008] In the prior art, antibodies or other reactants are bound to a chromatography matrix for example inside a micro flow cell for standard affinity chromatography or bound to a multi well plate for standard enzyme linked immunosorbent assay (ELISA), before being washed round with reactants.

[0009] In standard spotted micro arrays, reactants are spotted or printed onto a carrier matrix, made of glass for example, where they bind or adhere to the surface.

[0010] The United States patent application US 2015/276728 A1 discloses disposable tips comprising mechanically immobilized beads, wherein the beads are lined up in the front part of a plastic tip for washing around with reactants.

[0011] Furthermore, pre-dispensed reagent cartridges are known for single arrays for example to extract DNA or RNA with paramagnetic particles.

Object of the invention

[0012] The present invention shall provide a receptacle and a method for facilitated in vitro diagnostic applications minimizing the number of potential error sources.

Summary of the invention

[0013] The instant invention provides a receptacle comprising at least one immobilized assay component for an in-vitro diagnostic application. The immobilized assay component may adhere evenly to the receptacle's inner surface and may comprise bio-reactive particles. The bio-reactive particles might be magnetic beads.

[0014] In a further aspect, the assay component may be attached to the inner surface of the receptacle in a paste-like form, as a gel pastille, as a tablet or as a lyophilized coat application.

[0015] The assay component may comprise at least component selected from the group comprising drugs, chemical or bio-chemical substances, amino-acids, peptides, proteins, nucleic acids, carbohydrates, antibodies, lipids, micelles, vesicles, synthetic molecules, polymers, metal particles, nanoparticles, a solid phase cells, micro-organisms, viruses and magnetic particles.

[0016] Magnetic particles may further comprise at least one functional group selected from the group comprising peptides, nucleic-acids, monoclonal or polyclonal anti-bodies.

[0017] Magnetic particles can be non-covalently bound to a ligand interacting with at least one of a receptor, enzyme, metal compley or chemical or bio-chemical complex.

[0018] In a further aspect of the invention it is intended that the immobilized assay component is soluble in an aqueous solution.

[0019] It is intended that the immobilized assay component is water-soluble and that the immobilized assay component is immobilized with at least one immobilizing component of the group comprising monosaccharides, oligosaccharides, polysaccharides and gelatinizing agents.

[0020] A gelatinizing agent might be selected from the group comprising agarose, agar and gelatin.

[0021] Furthermore, the receptacle may be part of a cartridge comprising at least one further assay component or the receptacle is a tube, a bottle, a multi-well plate, a vial with lid or a cuvette.

[0022] The instant invention further provides a method of carrying out an in-vitro diagnostic assay comprising the steps of immobilizing at least one assay component evenly with at least one immobilizing component selected from the group comprising monosaccharides, oligosaccharides, polysaccharides and gelatinizing agents.

[0023] The assay component may be immobilized by surface drying, lyophilization, gelation, or dissolving in highly viscous medium.

[0024] The immobilizing step may comprise the step of applying the assay component in pasty or lyophilized form to the receptacle.

[0025] The step of bringing the immobilized assay component into the receptacle may comprises the step of inserting the immobilized assay component into the receptacle in form of an effervescent tablet or gel pastille.

[0026] Moreover, the liquid assay component might be a patient sample or a buffer.

Detailed description of the invention

[0027] The present invention provides a receptacle and method for facilitated in vitro diagnostic applications with a minimized number of potential error sources.

[0028] According to the present invention, at least one of the reactants, for example the beads, is immobilized in the reaction vessel by applying the reactant in pasty or lyophilized form onto the vessel wall or by inserting the reactant into the receptacle in form of an effervescent tablet or gel pastille. The immobilization of the reactants may be carried out by surface drying, lyophilization, gelation, or dissolving in highly viscous medium.

[0029] The immobilization of the reactants and the ensuring of their correct concentration are integrated into the production process of the reaction vessel.

[0030] The immobilization of reactants in the reaction vessel greatly minimizes the risk of a potential biological hazard by leakage of a liquid during transport. The risk is smallest, when all reactants are immobilized in the reaction vessel. In addition, has the spatial orientation of the reaction vessel during transport and storage no subsequent effects on the functionality and the reaction behavior, if the reactants are immobilized. Furthermore can mistakes due to evaporation not occur, since the immobilized reactants in the reaction vessel are liquid-free.

[0031] The immobilized reactants must be re-suspended before or during the reaction. For re-suspension a patient sample or a suitable buffer can be used. Alternatively, another reactant which is either a component of the reaction mixture or is additionally introduced for this step can be used for re-suspending immobilized reactants.

[0032] As a result, the reaction components, preferably the beads, can be distributed more homogeneously and the reliability of the reaction increases. Likewise, the throughput time of the reaction can be markedly reduced by an automated process. Many time-consuming preparation and distribution steps are omitted, so that the process becomes significantly faster. Automation solutions can be simplified and thus be more cost-effective, because the additional mixing of the reactants, as for example the beads, is no longer necessary.

[0033] The reaction vessel may also be part of a complex reaction cartridge which may contain further solid or liquid reactants necessary for the reaction.

[0034] In one embodiment, magnetic beads with a reactive surface for specifically binding and detecting biomolecules are transferred into reaction vessels in aliquots. The goal is that each reaction vessel contains the same amount of corresponding beads and that these beads are immobilized in the vessel in such a way that they can't be lost through motion during transport and loading of the device. Furthermore, the immobilizing component is at best suitable for stabilizing the beads such that they can be stored and transported at room temperature for a certain time. In addition, the immobilizing component is highly water soluble, which means that the immobilized beads can be re-suspended with the reaction buffer system. Various mono-, oligo- and polysaccharides, as for example trehalose, are conceivable as immobilizing and stabilizing components. These glutinous sugars can be dried or

lyophilized. However, it is also possible to use gelling substances such as agarose, agar, gelatin or the like. Important for all immobilizing components, including adhesives and fixatives, is a good solubility in a known aqueous buffer for example over water solubility, pH-dependent solubility or solubility by denaturing salts.

[0035] In the present invention, the beads are immobilized in the reaction vessel before being transported in the finished reaction vessel. The beads are re-suspended before the reaction. As a result, a separate transport vessel and a pipetting step can be saved.

[0036] According to the present invention, in vitro diagnostic applications include assays. An assay is an analytic procedure for qualitatively or quantitatively measuring for instance the presence, amount, and/or functional activity of an analyte. Analytes include, but aren't limited to, chemical or biochemical molecules, viruses, microorganisms and cells.

[0037] Reactions may be of biochemical or chemical type and include enzymatic, magnetic, luminescent, fluorescent, color change and binding reactions.

[0038] Reaction vessels according to the present invention include manifold receptacles such as micro titer and multi well plates as well as tubes, cuvettes and reaction vials with or without lids. Transport vessels may be chosen from the group comprising but not limited to cartridges, bottles, vials, tubes, cuvettes, well plates, and pipetting tips.

[0039] The pipetting needles may be disposable pipetting tips or can be made of steel for repeated use.

[0040] According to the present invention, assay components include bio-reactive particles. Bio-reactive particles have a specific reactive surface for binding biomolecules and include functionalized beads. Such beads can be functionalized for example with chemical or biochemical molecules, viruses, microorganisms and cells. Biochemical molecules include nucleic acid molecules such as DNA and RNA, as well as amino acid molecules such as peptides and proteins. Moreover, particles and beads can be magnetic. Chemical molecules include metals. Further assay components include patient samples buffers and other reactants.

[0041] Liquid solutions may for example be suspensions or liquids comprising a solved agent.

[0042] The advantages of the invention of the present disclosure can be summarized as follows:

- By immobilizing at least one of the reactants in the reaction vessel already, a separate transport vessel and at least one pipetting step are saved. Furthermore, reactants like beads don't need to be re-suspended before pipetting;
- By omitting an additional pipetting step, the potential errors such as all pipetting errors for example related to foam, clots, incorrect pipetting and system-related errors are eliminated;
- Detrimental influences from packaging and/or storage fluids can be reduced;
- Stirring and mixing of the beads in their storage vessel before adding them to the reaction vessel is omitted. Storage vessels suitable for stirring are therefore no longer required; and
- Due to the immobilization of the reactants, such as beads, in the reaction vessel, the spatial orientation of the transport vessel is less important during transportation. The beads can no longer dry on the lid or in a gap, neither can they spill when the vessel is opened. All of the beads can therefore be re-suspended at any time and the yield is thereby ensured.

CLAIMS

1. Ein Behälter, umfassend mindestens eine Assaykomponente für eine in-vitro-diagnostische Anwendung, die an einer inneren Oberfläche des Behälters immobilisiert ist und anhaftet.

2. Der Behälter nach Anspruch 1, dadurch gekennzeichnet, dass die Assaykomponente an der inneren Oberfläche des Behältnisses in pastenartiger Form, als Gelpastille, als Tablette oder als lyophilisierte Beschichtungsapplikation angebracht ist.

3. Der Behälter nach einem der Ansprüche 1 oder 2, wobei die immobilisierte Assay-Komponente mindestens eine Komponente ist, ausgewählt aus der Gruppe umfassend Arzneimittel, chemische oder biochemische Substanzen, Aminosäuren, Peptide, Proteine, Nukleinsäuren, Kohlenhydrate, Antikörper umfasst Lipide, Micellen, Vesikel, synthetische Moleküle, Polymere, Metallpartikel, Nanopartikel, Festphasen-Zellen, Mikroorganismen, Viren und magnetische Partikel.

4. Der Behälter nach Anspruch 4, wobei die magnetischen Partikel mindestens eine funktionelle Gruppe umfassen, ausgewählt aus der Gruppe umfassend Peptide, Nukleinsäuren, monoklonale oder polyklonale Antikörper.

5. Der Behälter nach einem der Ansprüche 3 bis 6, wobei die magnetischen Partikel nicht-kovalent an einen Liganden gebunden sind, der mit mindestens einem von einem Rezeptor, einem Enzym, einem Metallkomplex oder einem chemischen oder biochemischen Komplex interagiert.

6. Der Behälter nach einem der Ansprüche 1 bis 5, wobei die immobilisierte Assaykomponente in einer wässrigen Lösung löslich ist.

7. Der Behälter nach einem der Ansprüche 1 bis 6, wobei die immobilisierte Assaykomponente mit mindestens einer immobilisierenden Komponente immobilisiert ist, ausgewählt aus der Gruppe umfassend Monosaccharide, Oligosaccharide, Polysaccharide und Geliermittel.

8. Der Behälter nach Anspruch 7, wobei das Geliermittel ausgewählt ist aus der Gruppe umfassend Agarose, Agar und Gelatine.

9. Der Behälter nach einem der Ansprüche 1 bis 8, wobei der Behälter Teil einer Kartusche ist, die mindestens eine weitere Assaykomponente umfasst oder ein Röhrchen, eine Flasche, eine Multi-Well-Platte, eine Ampulle mit Deckel oder eine Küvette ist.

10. Der Behälter nach einem der Ansprüche 1 bis 9, wobei der Behälter aus einem Material besteht, ausgewählt aus der Gruppe umfassend Kunststoff, Glas oder Metall.

11. Eine Verwendung eines Behälters nach einem der Ansprüche 1 bis 10 zur Durchführung eines Assays.

12. Ein Verfahren zum Immobilisieren einer Assaykomponente, umfassend den Schritt des Immobilisierens der Assaykomponente mit mindestens einer stabilisierenden Komponente, ausgewählt aus der Gruppe umfassend Monosaccharide, Oligosaccharide, Polysaccharide und Geliermittel.

13. Das Verfahren nach Anspruch 12, wobei die Assaykomponente bio-reaktive Partikel umfasst.

14. Das Verfahren nach Anspruch 12 oder 13, wobei der Immobilisierungsschritt ferner Oberflächentrocknen, Lyophilisieren, Gelieren oder Auflösen in hochviskosem Medium beinhaltet.

15. Das Verfahren nach einem der Ansprüche 12 bis 14, wobei der Immobilisierungsschritt ferner den Schritt des Aufbringens der Assaykomponente in pastöser oder lyophilisierter Form auf die Behälterwand oder -boden umfasst.

16. Das Verfahren nach einem der Ansprüche 12 bis 15, wobei der Immobilisierungsschritt weiterhin den Schritt des Einbringens der immobilisierten Assaykomponente in das Behältnis in Form einer Brausetablette oder Gelpastille umfasst.

ABSTRACT

The invention relates to a receptacle and method for in vitro diagnostic applications. The present invention facilitates in vitro diagnostic applications and minimizes the number of potential error sources by providing a receptacle with an immobilized assay component that can be re-suspended.

LE GOUVERNEMENT
DU GRAND-DUCHÉ DE LUXEMBOURG
Ministère de l'Économie

National Application Number

LO 1905
LU 100716

SEARCH REPORT

in accordance with Article 35.1 a)
of the Luxembourg law on patents
dated 20 July 1992

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	WO 02/090983 A2 (MEDSYSTEMS DIAGNOSTICS GMBH [AT]; RECH-WEICHSELBRAUN IRENE [AT]; SCHAU) 14 November 2002 (2002-11-14) * paragraph [0001]; claims 1-7 * * paragraph [0031] - paragraph [0032] *	1,3,6, 9-11	INV. G01N33/543
X Y	US 2003/108973 A1 (GATTO-MENKING DEBORAH L [US] ET AL) 12 June 2003 (2003-06-12) * claims 1-13 *	1-3,6, 9-11 1-16	
X	US 2005/048667 A1 (ELLMAN BRETT [US] ET AL) 3 March 2005 (2005-03-03) * paragraph [0044] - paragraph [0055]; claims 1-33 *	1-15	
X	US 2005/164408 A1 (BOSS GERRY R [US] ET AL) 28 July 2005 (2005-07-28) * the whole document *	1-14	
X	WO 2006/137787 A1 (GE HEALTHCARE BIO SCIENCES AB [SE]; ALGOTSSON MATTIAS [SE]; GLAD GUNNA) 28 December 2006 (2006-12-28) * the whole document *	1-14	TECHNICAL FIELDS SEARCHED (IPC) G01N
X Y	US 2015/218613 A1 (DE FOREST NIKOL [US] ET AL) 6 August 2015 (2015-08-06) * paragraph [0144] - paragraph [0149]; claims 1-47 *	1-3,6, 9-11 1-16	

The present search report has been drawn up for all claims

	Date of completion of the search	Examiner
	24 May 2018	Moreno de Vega, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C09)

ANNEX TO THE SEARCH REPORT ON LUXEMBOURG PATENT APPLICATION NO.

LO 1905
LU 100716

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

24-05-2018

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		WO 2015164746 A1	29-10-2015

LE GOUVERNEMENT
DU GRAND-DUCHÉ DE LUXEMBOURG
Ministère de l'Économie

WRITTEN OPINION

File No.	Filing date *(day/month/year)*	Priority date *(day/month/year)*	Application No.
LO1905	26.02.2018		LU100716

International Patent Classification (IPC)
INV. G01N33/543

Applicant
STRATEC BIOMEDICAL AG

This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the application
- ☒ Box No. VIII Certain observations on the application

Form LU237A (Cover Sheet) (January 2007)

Examiner
Moreno de Vega, C

Application No.
LU100716

WRITTEN OPINION

Box No. I Basis of the opinion

1. This opinion has been established on the basis of the latest set of claims filed before the start of the search.

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ on paper

   ☐ in electronic form

   c. time of filing/furnishing:

   ☐ contained in the application as filed.

   ☐ filed together with the application in electronic form.

   ☐ furnished subsequently.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty	Yes:	Claims	16
	No:	Claims	1-15
Inventive step	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION

Box No. VIII Certain observations on the application

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Reference is made to the following documents:

D1 WO 02/090983 A2 (MEDSYSTEMS DIAGNOSTICS GMBH [AT]; RECH-WEICHSELBRAUN IRENE [AT]; SCHAU) 14 November 2002 (2002-11-14)

D2 US 2003/108973 A1 (GATTO-MENKING DEBORAH L [US] ET AL) 12 June 2003 (2003-06-12)

D3 US 2005/048667 A1 (ELLMAN BRETT [US] ET AL) 3 March 2005 (2005-03-03)

D4 US 2005/164408 A1 (BOSS GERRY R [US] ET AL) 28 July 2005 (2005-07-28)

D5 WO 2006/137787 A1 (GE HEALTHCARE BIO SCIENCES AB [SE]; ALGOTSSON MATTIAS [SE]; GLAD GUNNA) 28 December 2006 (2006-12-28)

2 The present application does not meet the criteria of patentability, because the subject-matter of claims 1-15 is not new.

2.1 Document D1, see especially the claims, discloses an immunological test kit, for quantitative or qualitative determination of a substance (I), comprising a multiwell carrier or microtiter plate coated with a primary binding partner (BP1) immobilized as lyophilizate and in some of the wells, a series (incremental dilutions) of a reference standard of (I), also lyophilized. BP1 is e.g. an antibody, antigen, receptor or ligand. Optionally the wells also include lyophilized sample dilution buffer. D1 is novelty destroying for claims 1, 3, 6, 9-11.

2.2 Document D2, see especially the claims, teaches a reagent comprising an immobilized capture antibody and a labeled reporter antibody, which are bound specifically to same analyte. The reagent mixture is prepared by drying

a liquid mixture containing labeled reporter antibody in presence of immobilized capture antibody. Said drying is carried out by lyophilization. D2 also discloses a kit comprising the reagent in a container.

D2 is novelty destroying for claims 1-3, 6, 9-11.

2.3 Document D3, see claims and paragraphs 0044-0055, discloses a method of forming a solid-phase support, the method including the steps of providing a substrate having a reaction vessel, dispensing particles in the reaction vessel, and permanently bonding the particles in the substrate within the reaction vessel. The particles may include a microbead, and may be made of e.g. glass, plastic, polystyrene, resin, gel, agarose, sepharose. The particles can be embedded into the substrate, or can be adhesively bonded to the internal surface of the well utilizing a thermoplastic material having a relatively low melting point, a two-part epoxy, and/or other suitable means.

D3 is novelty destroying for claims 1-15.

2.4 Document D4, see especially the claims, teaches a method for isolating of analyte comprising coating an inner wall of a test tube with beads; coating the beads with a capture reagent; incubating the coated beads with a solution containing analyte to allow binding of analyte to the binding partner; washing the coated beads with the bound analyte with a wash buffer to remove unbound material while maintaining the binding; and eluting analyte from the binding partner. The beads may be made of e.g. glass, polymer, agarose. D4 is novelty destroying for claims 1-14

2.5 Document D5 discloses a method for performing small scale cell culture, cell screening or cell assaying by using microcarrriers and cell screening tool. The microcarriers are attached to the solid phase by mechanical interlocking or interdiffusion of polymer chains, through chemical or biological bonding, hydrophobic interaction to the solid support, or via liquid adhesive to inert surface. Said microcarriers are provided with ligands having interaction, such as affinity, for specific cells or cell structures. The solid phase is microtiter plate provided with multiple wells, where each well is provided with immobilized particles. The particles or microcarriers are coated with adhesion factor, such as gelatin, fibronectin, laminin, collagen, vitronectin or tenascin.

D5 is novelty destroying for claims 1-14.

3 The present application does not meet the criteria of patentability, because the subject-matter of claim 16 does not involve an inventive step.

The feature of introducing an assay component in form of a tablet in a receptacle or container is described in document D6, see claim 47 and paragraphs 0144 to 0149, as providing the same advantages as in the present application. The skilled person would therefore regard it as a normal design option to include this feature in the container described in D2 in order to solve the problem posed.

Re Item VIII

Certain observations on the application

4 Present claims are not clear.

The term "assay component" used in present claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claims unclear. Said term encompasses any possible form of reagent, molecule, material, sample, etc that might be part of any in vitro assay or determination