Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2683920 C 2016/05/31

(11)(21) **2 683 920**

(12) **BREVET CANADIEN**
CANADIAN PATENT

(13) **C**

(86) **Date de dépôt PCT/PCT Filing Date:** 2008/04/15
(87) **Date publication PCT/PCT Publication Date:** 2008/10/23
(45) **Date de délivrance/Issue Date:** 2016/05/31
(85) **Entrée phase nationale/National Entry:** 2009/10/14
(86) **N° demande PCT/PCT Application No.:** SE 2008/050424
(87) **N° publication PCT/PCT Publication No.:** 2008/127191
(30) **Priorités/Priorities:** 2007/04/16 (SE0700930-1); 2007/04/16 (US60/923,798)

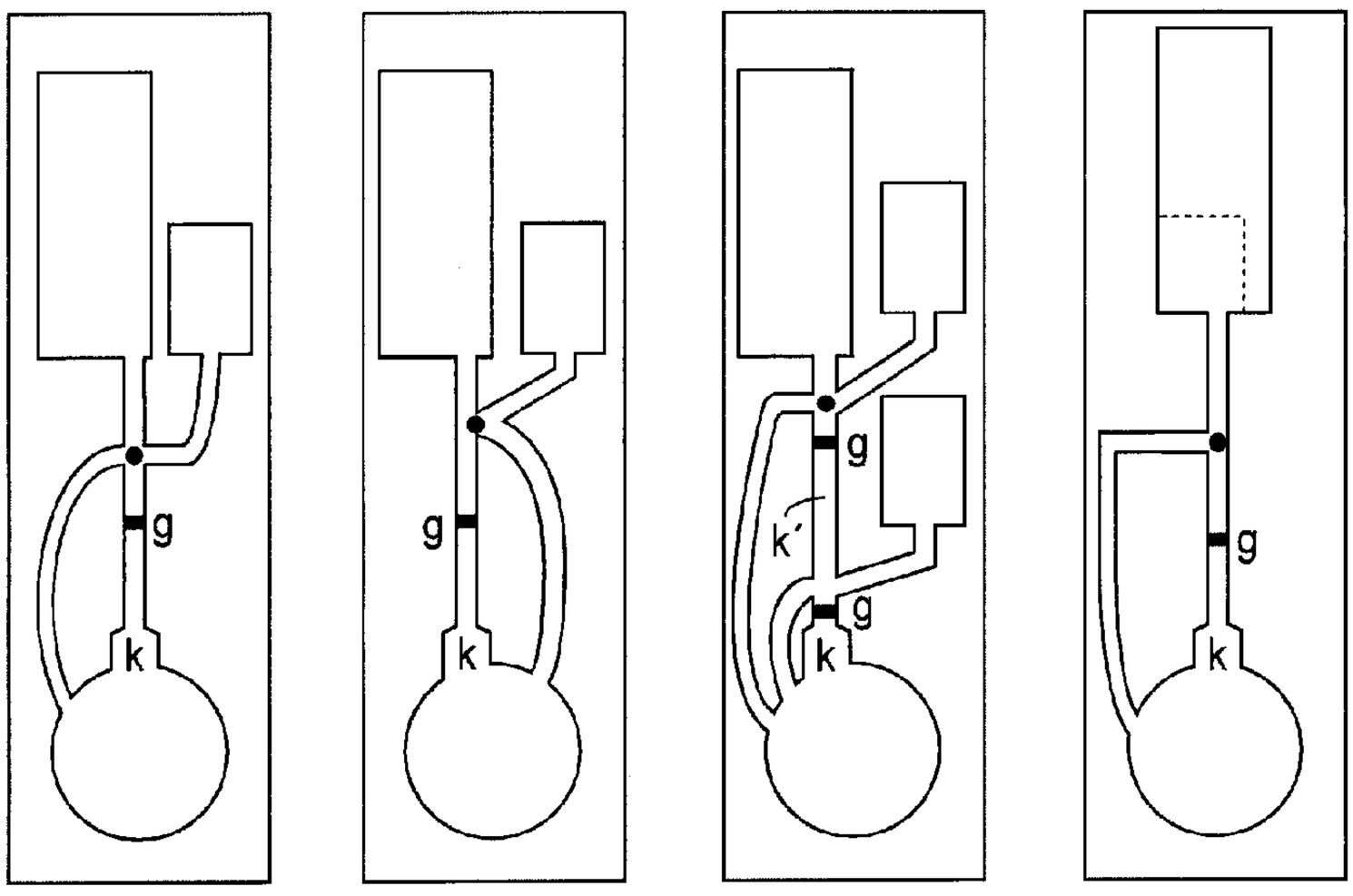
(51) **Cl.Int./Int.Cl.** ***B01L 3/00*** (2006.01)

(72) **Inventeurs/Inventors:**
BERGMAN, DAVID, SE;
KREUEGER, PIERRE, SE;
ROENNHOLM, DAVID, SE

(73) **Propriétaire/Owner:**
AMIC AB, SE

(74) **Agent:** NORTON ROSE FULBRIGHT CANADA LLP/S.E.N.C.R.L., S.R.L.

(54) **Titre : DISPOSITIF POUR LA MANIPULATION D'ECHANTILLONS DE LIQUIDE**
(54) **Title: DEVICE FOR HANDLING LIQUID SAMPLES**



(57) **Abrégé/Abstract:**
There is disclosed a device for handling liquid samples, said device comprising: a) projections substantially perpendicular to the surface of said device, said projections having a height, diameter and a distance between the projections capable of generating capillary flow, lateral to said surface, of a fluid, b) at least one zone for receiving a sample, c) at least one sink with a capacity of receiving said liquid, said at least one sink exerting at least two different capillary forces on said liquid, d) at least two flow paths connecting said at least one zone for receiving a sample and said at least one sink, said flow paths exerting at least two different capillary forces on said liquid, e) at least one connection between said at least two flow paths.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 October 2008 (23.10.2008)

PCT

(10) International Publication Number
WO 2008/127191 A1

(51) International Patent Classification:
B01L 3/00 (2006.01)

(21) International Application Number:
PCT/SE2008/050424

(22) International Filing Date: 15 April 2008 (15.04.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/923,798 16 April 2007 (16.04.2007) US
0700930-1 16 April 2007 (16.04.2007) SE

(71) Applicant *(for all designated States except US)*: **ÅMIC AB** [SE/SE]; Uppsala Science Park, S-751 83 Uppsala (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BERGMAN, David** [SE/SE]; Boängsvägen 52F, S-741 92 Knivsta (SE). **KREÜGER, Pierre** [SE/SE]; Götgatan 20 B, S-752 22 Uppsala (SE). **RÖNNHOLM, David** [SE/SE]; Arenbergavägen 10, S-195 42 Märsta (SE).

(74) Agent: **BERGENSTRÅHLE & LINDVALL AB**; Fredrik Carlsson, Box 17704, S-118 93 Stockholm (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(54) Title: DEVICE FOR HANDLING LIQUID SAMPLES

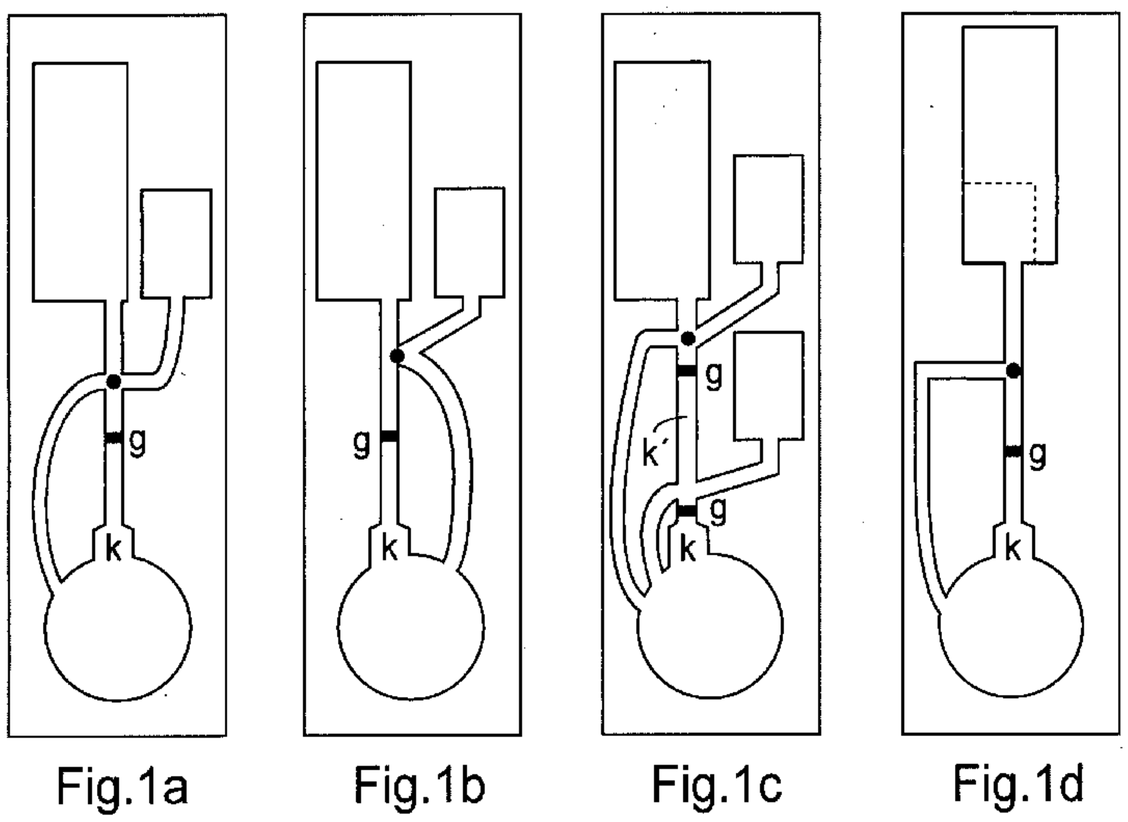


Fig.1a Fig.1b Fig.1c Fig.1d

(57) Abstract: There is disclosed a device for handling liquid samples, said device comprising: a) projections substantially perpendicular to the surface of said device, said projections having a height, diameter and a distance between the projections capable of generating capillary flow, lateral to said surface, of a fluid, b) at least one zone for receiving a sample, c) at least one sink with a capacity of receiving said liquid, said at least one sink exerting at least two different capillary forces on said liquid, d) at least two flow paths connecting said at least one zone for receiving a sample and said at least one sink, said flow paths exerting at least two different capillary forces on said liquid, e) at least one connection between said at least two flow paths.

WO 2008/127191 A1

Device for handling liquid samples

Technical field

[0001] The present invention relates to the field of devices for handling liquid samples.

Background

[0002] Devices for handling liquid samples of various kinds are desirable to use for instance within point of care analyses. Moreover such devices can be used to analyse various samples including of blood, plasma, serum, sweat, saliva, urine, lachrymal fluid, water samples, and suspensions or solutions of food samples.

[0003] Such assay devices are described in for instance WO 2005/118139 (ÅMIC AB), WO 2005/089082 (ÅMIC AB), and WO 03/103835 (ÅMIC AB).

[0004] Other assay devices are described in for instance US 5,458,852 (BIOSITE) and EP 1120164 (ROCHE DIAGNOSTICS GMBH).

[0005] GB 2410086 (BRITISH BIOCELL INTERNAT LTD) discloses an assay device comprising a flow block to determine flow of liquids.

[0006] US 6,296,020 (BIOMICRO SYSTEMS, INC.) discloses methods of controlling fluid flow through micro channels by use of passive valves or stopping means.

Disclosure of the invention

Technical problem

[0007] In some of the known assay devices a sample comprising an analyte is added, which sample flows along a flow path where a dried reagent is dissolved. The sample now comprising the reagent flows to an analysis point where the sample is analysed with regards to one or more properties. This type of technology has a number of problems.

[0008] One problem concerning the above mentioned technique is how to let the sample reach the analysis point before the reagent. This is desired in some applications.

[0009] Another problem is how to accurately and reproducible define a certain volume of sample which passes the analysis point before the reagent reaches the analysis point.

[0010] Another problem is how to let the sample react at the analysis point for a prolonged time before the reagent reaches the analysis point.

[0011] A further problem is to eliminate effects from the fact the reagent may dissolve differently depending on for instance age of the reagent and how dry the reagent is.

[0012] The measured signal in some assays depends on the amount of reagent and the amount of sample. In many assays some kind of particles and/or some kind of molecules are detected and therefore the sample volume must be well defined.

Technical solution

[0013] It is an object of the present invention to alleviate at least some of the problems in the state of the art.

[0014] This is achieved by using the present invention which in a first aspect provides a device for handling liquid samples, said device comprising: a) projections substantially perpendicular to the surface of said device, said projections having a height, diameter and a distance between the projections capable of generating capillary flow, lateral to said surface, of a fluid, b) at least one zone for receiving a sample, c) at least one sink with a capacity of receiving said liquid, said at least one sink exerting at least two different capillary forces on said liquid, d) at least two flow paths connecting said at least one zone for receiving a sample and said at least one sink, said flow paths exerting at least two different capillary forces on said liquid, e) at least one connection between said at least two flow paths.

[0015] The assay device utilises projections substantially perpendicular to the surface to create a capillary force so that the liquid flows. The device utilises the fact that the capillary force can be different for different flow channels depending on the distance, geometry, diameter, and height of the projections. The difference in capillary force is used to direct the flow in the desired direction.

[0016] Also encompassed within the present invention is a method of analysing a sample as well as a kit of parts.

Advantageous effects

[0017] Advantages of the present invention include that it is possible to let a sample reach an analysis point before a reagent. Another advantage is that it is possible to define a certain volume of sample that passes an analysis point before the reagent reaches the analysis point. A further advantage is that it is possible to eliminate or alleviate effects from reagents which dissolve differently.

Brief description of the drawings

[0018] Fig 1a-d depicts various embodiments of devices according to the present invention.

[0019] Fig 2a-d depicts various stages during use of a device according to the present invention.

[0020] Fig 3 is an electron micrograph of a part of an analysis device according to the present invention. It depicts a cross of two flow channels as used for instance in the device depicted in Fig 2.

[0021] Fig 4 depicts a section of a flow channel comprising a gate which can be used in an assay device according to the present invention.

Definitions

[0022] Before the invention is disclosed and described in detail, it is to be understood that this invention is not limited to particular configurations, process steps, and materials disclosed herein as such configurations, process steps, molecules, and materials may vary somewhat. It is also to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting since the scope of the present invention is limited only by the appended claims and equivalents thereof.

[0023] It must be noted that, as used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise. The following terms are used throughout the description and the claims.

[0024] “Analysis” is used herein to denote the process where a sample is examined to gain an understanding of it, regarding for instance its qualitative and/or quantitative composition.

[0025] “Analysis point” is used herein to denote a point or an area on an assay device where a measurement is performed.

[0026] “Analyte” is used herein to denote a substance, chemical constituent, or biological constituent that is analysed.

[0027] “Reagent” is used herein to denote a chemical or biological constituent participating in the analysis.

[0028] “Sample” is used herein to denote any matter comprising an analyte.

Detailed description

[0029] At least some of the above mentioned advantages are achieved by using an assay device of a special design. The assay device utilises projections substantially perpendicular to the surface to create a capillary force so that the liquid flows. The assay device assay utilises the fact that the capillary force can be different for different flow channels depending on the distance, geometry, diameter, and height of the projections. The difference in capillary force is used to direct the flow in the desired direction.

[0030] In one embodiment depicted in Fig 1a the device for handling liquid samples comprises one zone for receiving a sample, shown as the circular zone. There are two separate rectangular sinks with a capacity of receiving said liquid, and two flow paths each connected to one sink respectively, and one connection between said at least two flow paths. In this embodiment a reactant is dried onto the substrate on the area marked with a “k”. The embodiment further comprises a gate, which allows flow of liquid when it is in contact with liquid from at least two directions, indicated with a “g” in Fig 1.

[0031] It must be noted that such a gate only allows a flow of liquid when it is in contact with liquid from more that one side. An example of a gate which can be used in the present invention is depicted in Fig 4. It must be noted that the gates which can be used in the present invention is not limited to the gate depicted in Fig 4. Any type of gate can be used which blocks flow of liquid

when it is in contact with liquid from one side only and which allows flow of liquid when it is in contact with liquid from more than one side.

[0032] When liquid flows from the left to the right in the flow path depicted in Fig 4 the flow is blocked and when liquid flows from the right to the left the gate allows flow in both directions. A flow of liquid from the right to the left will flow in small flow paths in the side of the main flow path and will allow the liquid from both sides to join and thereby allows flow across the gate. This is possible to achieve when the capillary force of the gate is adapted to the intended liquid by adjusting the position, distance, geometry, diameter, and height of the projections as well as the width and positions of the smaller flow paths.

[0033] In one embodiment the gate comprises projections with adjusted positions, distance, geometry, diameter, and height.

[0034] In an alternative embodiment there is no gate. Instead the flow in at least one of the flow paths is made slower than in the other by making the flow path longer and/or lowering the capillary force exerted on the liquid.

[0035] The distance, geometry, diameter, and height of the projections is adapted so that the capillary force is higher in the at least a part of the flow path and one of the sinks as compared to the flow path leading to the other sink.

[0036] In one embodiment at least one reagent is adsorbed on the surface of at least one of the flow paths. In another embodiment the reagent is adsorbed on the flow path which exerts the lowest capillary force.

[0037] The flow paths exerting different capillary force on the liquid have in one embodiment different flow rates for the liquid, due to the different capillary force.

[0038] One embodiment of the cross of flow paths in Fig 2 is depicted in Fig 3 and consists in this particular embodiment of projections with different space to create different capillary force.

[0039] In one embodiment as depicted in Fig 1a there are two different sinks exerting different capillary forces on the liquid. In an alternative embodiment as depicted in Fig 1d there is one sink divided into two parts which are

exerting different capillary force on the liquid. The border between the parts is indicated with a dashed line in Fig 1d. When the part exerting the highest capillary force is completely filled the liquid will start to flow in the areas exerting a lower capillary force on the liquid so that the action is similar to that in Fig 1a and 1b.

[0040] In one embodiment a substance is adsorbed and/or bound to the analysis point. In one embodiment such a substance has the capability to bind to at least one analyte. Examples of such a substance include an antibody.

[0041] In one embodiment at least one reagent is adsorbed or dried onto at least one flow channel. Such a reagent can be any chemical or biological entity that is participating in an analysis. Examples of reagents include antibodies, antibodies comprising a detectable entity, other detectable molecules, and molecules with the ability to bind to an analyte.

[0042] In an alternative embodiment it is possible to perform a multistep analysis where for instance two, three or more reagents are added sequentially with a time difference. Such an embodiment is shown in Fig 1c, where two separate reagents k and k' are added after each other. In one embodiment at least three different capillary forces are exerted on said liquid; a first capillary force form a first sink, a second capillary force form a second sink and a third capillary force from a third sink. In one embodiment there are different sizes of the sinks shown in Fig 1c. In another embodiment the projections are adapted so that the exerted capillary force is different for the different sinks and flow paths.

[0043] In another embodiment it is possible to perform an analysis comprising two or more steps. In one embodiment an integrated analysis comprising three steps is performed. A specific example of such an analysis is a device according to Fig 1c, where a first antibody directed against the analyte is bound to the analysis point. In a first step the sample passes the analysis point and the analyte is bound to a fraction of the first antibodies on the surface. In the second step a second antibody directed against the analyte, which antibody comprises a general binding unit passes the analysis point. In the second

step the second antibody will bind to the analyte which is bound to the first antibodies at the analysis point. In a third step a detectable molecule with the capability of binding to the general binding unit on the second antibodies passes the analysis point. In the third step the detectable molecules are bound to the antibodies. An advantage of this three step analysis is that the third step is the same for all types of tests and that it thus can be optimised once for many different kinds of tests.

[0044] In a second aspect of the present invention there is provided a method of analysing a sample, wherein the analysis is performed using a device as described above. In such a method the sample is preferably added to the zone for receiving the sample. The method preferably comprises a step of reading a result of the analysis.

[0045] In a third aspect there is provided a kit of parts comprising the device as described above and at least one reagent. Optionally the kit of parts comprises a further assay device. Examples of such an assay device include a holder for the device, a measurement apparatus where said device is inserted or another device which facilitates the analysis. In one embodiment such kit of parts comprises at least one package. In another embodiment the kit of parts comprises a written instruction. In another embodiment the kit of parts comprises a reader capable of performing a measurement on said device. Such a reader may make a measurement on the analysis point.

[0046] When a liquid sample in one embodiment is added to the zone for receiving a sample, the liquid flows up to the gate in one flow path and a reagent is dissolved by the sample. This is depicted in Fig 2a. Black rectangles symbolises a reactant in Fig 2. In the other flow path the liquid flows into the zone for receiving a sample. The sample flows over the analysis point where the measurement is performed. Due to the higher capillary force in one of the flow paths the liquid flows along the flow path with the highest capillary force and fills the sink with the higher capillary force. Not until the sink with the higher capillary force is completely filled, the liquid will start to flow into the region with the lower capillary force. The time and the volume of sample that

passes the analysis point in the first step is defined by filling the sink with the higher capillary force. In Fig 2b the sink with the higher capillary force is completely filled and the sample starts to flow in the areas exerting a lower capillary force on the liquid.

[0047] The liquid will then flow towards the gate and when the gate thus is in contact with a liquid from both sides the liquid can flow across the gate in both directions. The liquid with the dissolved reactant will flow towards the other sink as depicted in Fig 2c. In Fig 2c it is shown that the dissolved reactant symbolised by a black rectangle passes the analysis point. In Fig 2d the measurement is completed and all sinks are completely filled and/or there is no more available sample volume. The time before the gate is opened can thus be well defined and the time is adjusted so that the reagent is allowed to dissolve to a sufficient degree.

CLAIMS:

1. A device for handling liquid samples, said device comprising: a) projections perpendicular to the surface of said device, said projections having a height, diameter and a distance between the projections for generating capillary flow, lateral to said surface, of a fluid, b) at least one zone for receiving a sample, c) at least one sink with a capacity of receiving said liquid, said at least one sink exerting at least two different capillary forces on said liquid, d) at least two flow paths connecting said at least one zone for receiving a sample and said at least one sink, said flow paths exerting at least two different capillary forces on said liquid, and e) at least one connection between said at least two flow paths.

2. The device according to claim 1 , wherein said at least one sink has two parts exerting different capillary force on said liquid.

3. The device according to claim 1 , comprising at least two different sinks each sink exerting a capillary force on said liquid, said capillary forces being different.

4. The device according to any one of claims 1-3, wherein at least one of said flow paths comprises at least one gate, which allows flow of liquid when it is in contact with liquid from at least two directions.

5. The device according to claim 4, wherein said gate further comprises projections perpendicular to the surface of said device.

6. The device according to any one of claims 1-5, wherein at least one reagent is adsorbed on at least one of said flow paths.

7. The device according to any one of claims 1-6, wherein at least one reagent is adsorbed on the flow path exerting the lowest capillary force on said liquid.

8. The device according to any one of claims 1-7, wherein said at least two flow paths have different flow rates for said liquid.

9. The device according to any one of claims 1-8, wherein said device exerts at least three different capillary forces on said liquid.

10. The device according to claim 9, wherein said device further comprises at least two different reagents.

11. A method of analysing a sample characterized in that a device according to any one of claims 1-10 is used, and wherein said sample is added to the at least one zone for receiving a sample.

12. The method according to claim 11 , wherein a result is read from said device.

13. A kit of parts comprising a device according to any one of claims 1-10 and at least one reagent.

14. The kit of parts according to claim 13 further comprising an analysis device.

15. The kit of parts according to any one of claims 13-14 further comprising at least one reader for performing a measurement on said device.

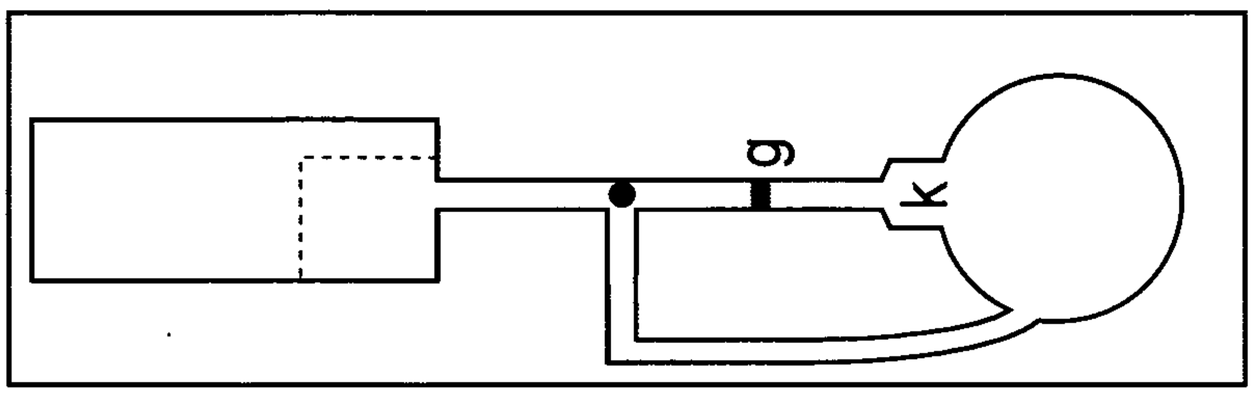


Fig.1d

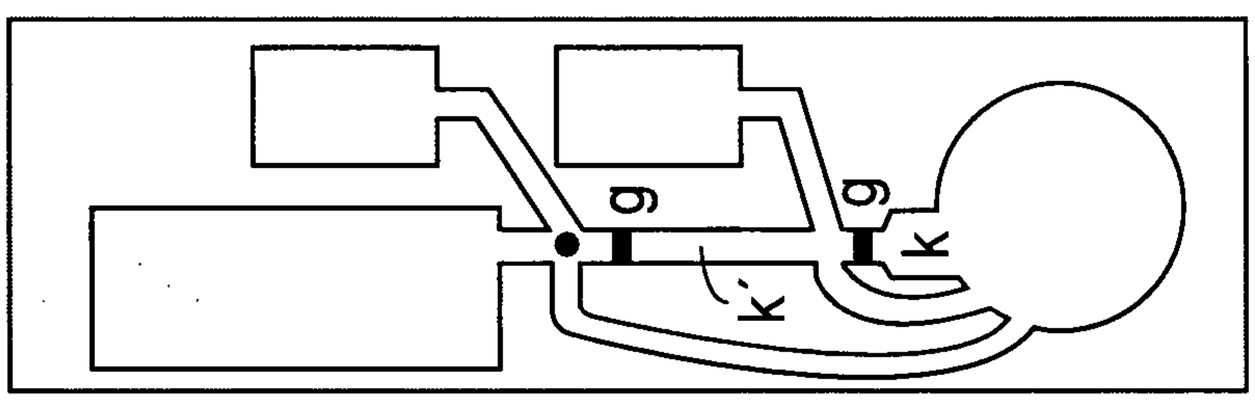


Fig.1c

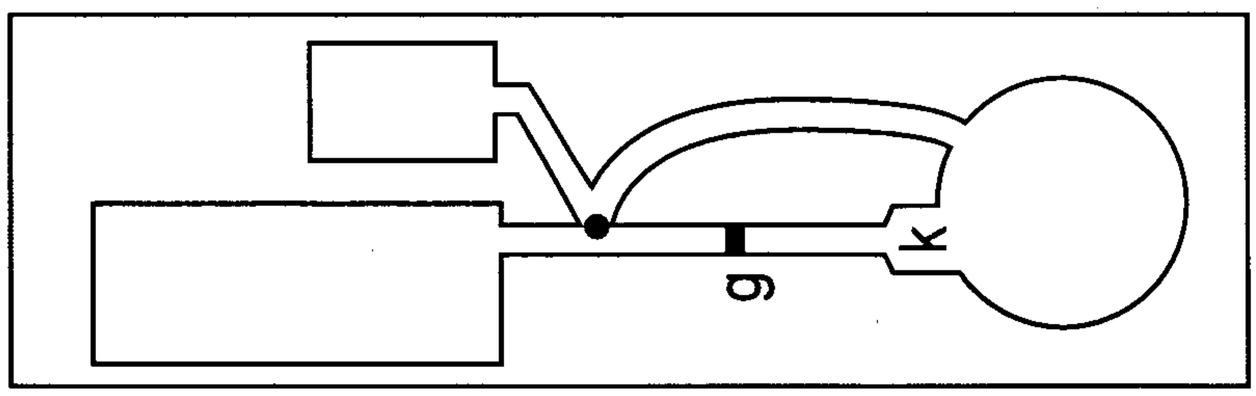


Fig.1b

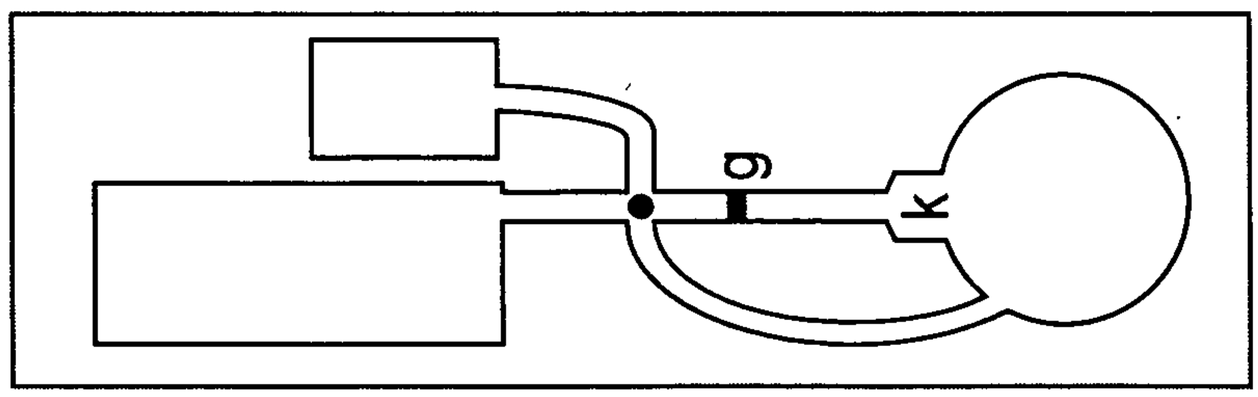


Fig.1a

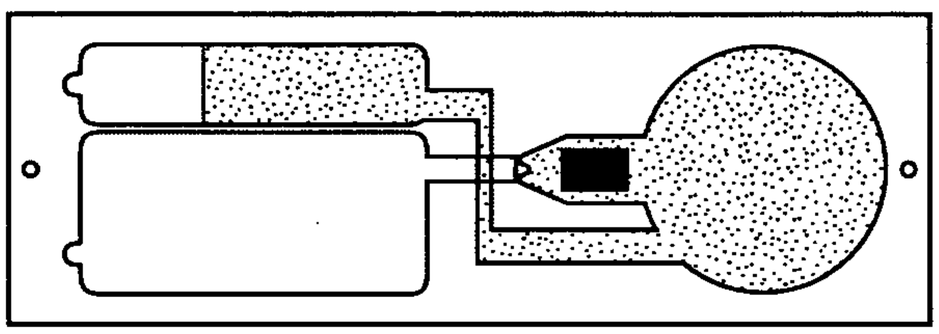


Fig.2a

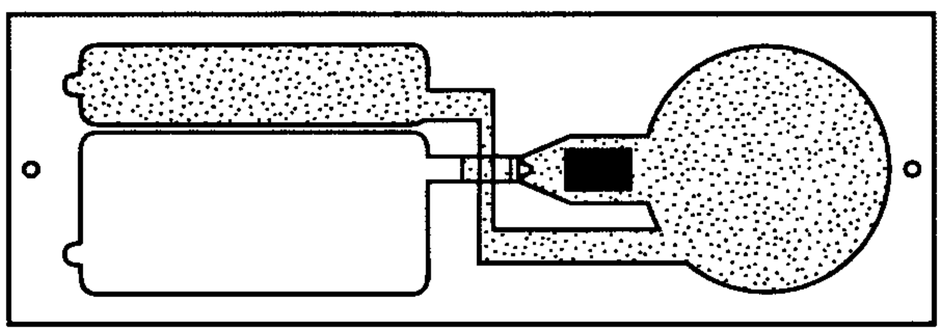


Fig.2b

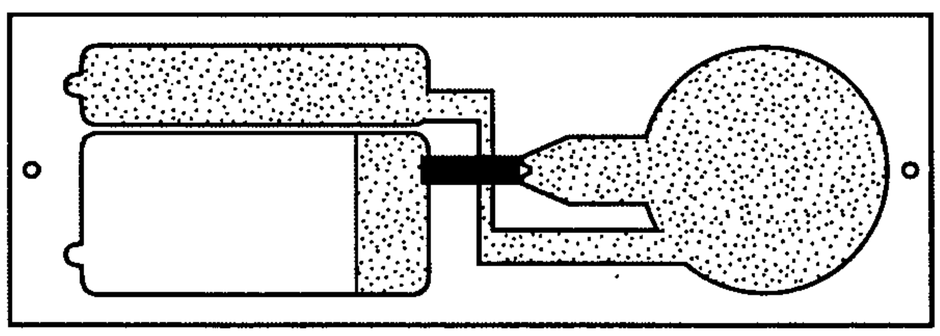


Fig.2c

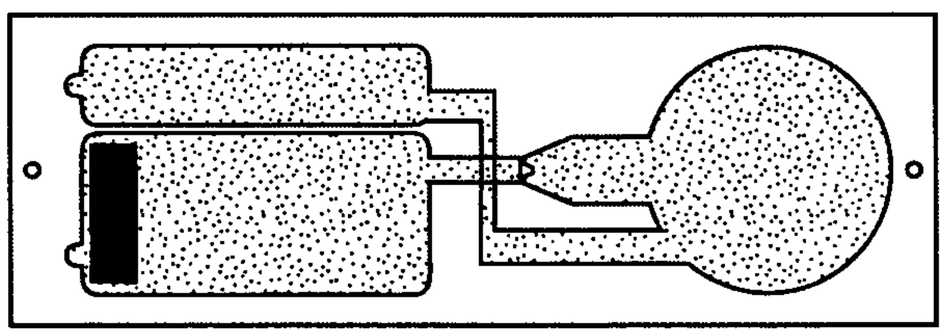


Fig.2d

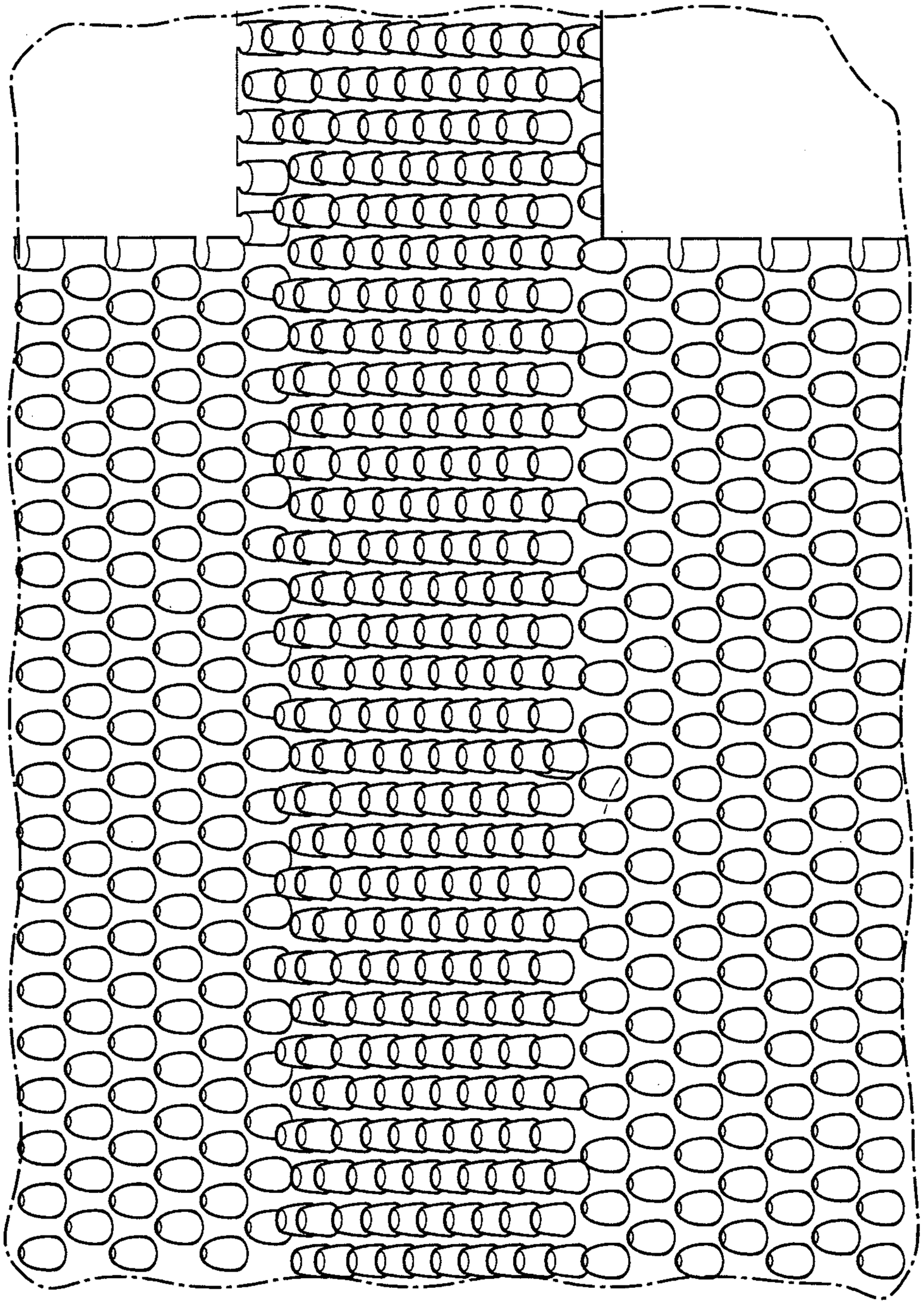


Fig 3

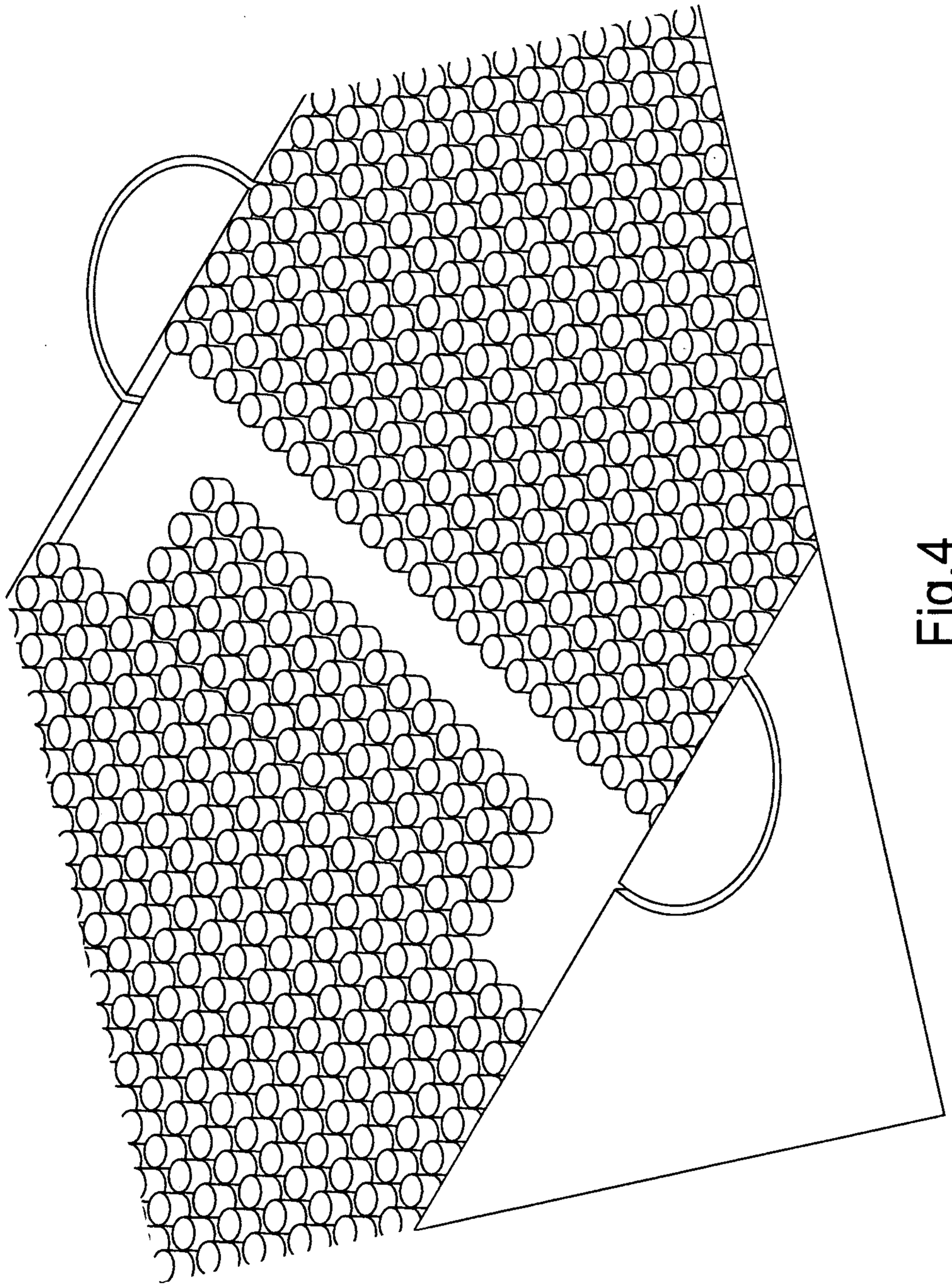
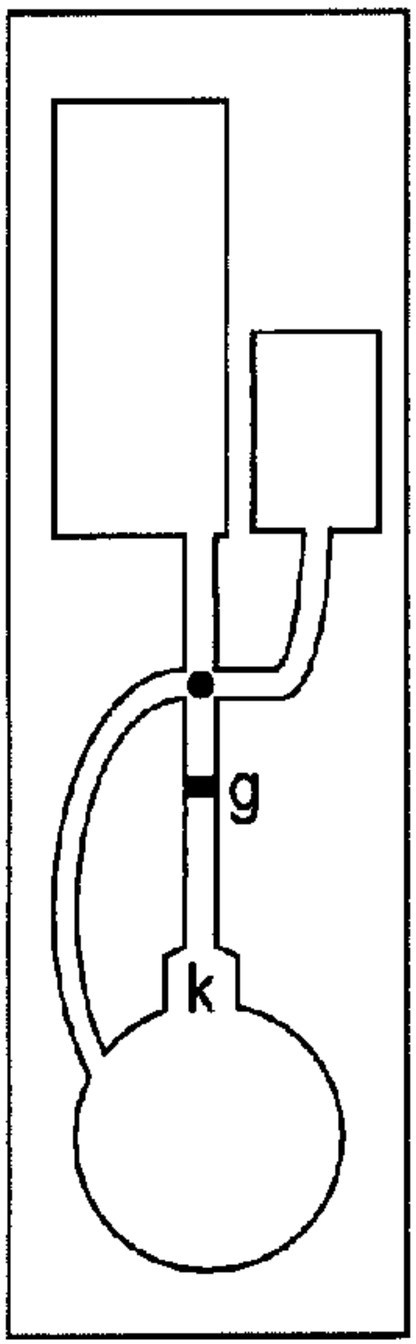
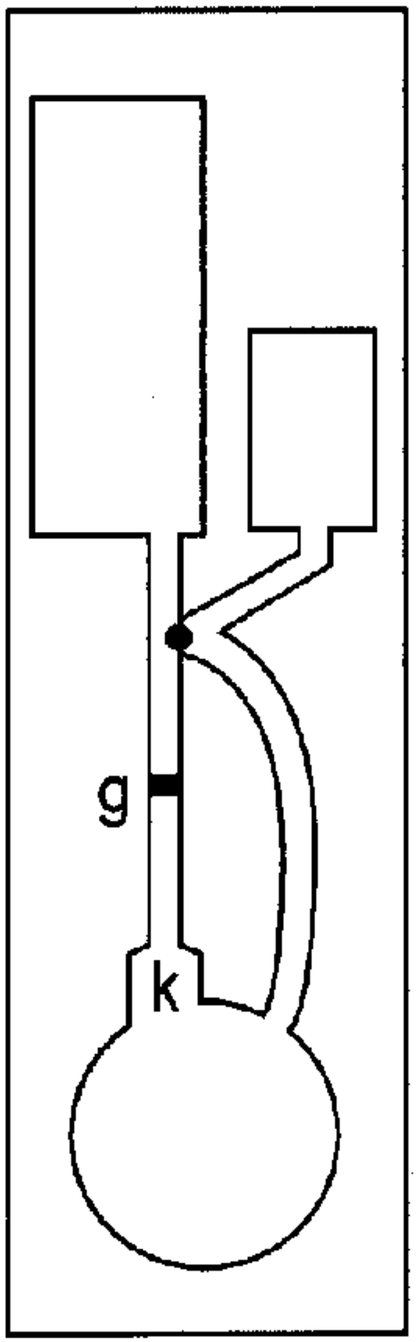


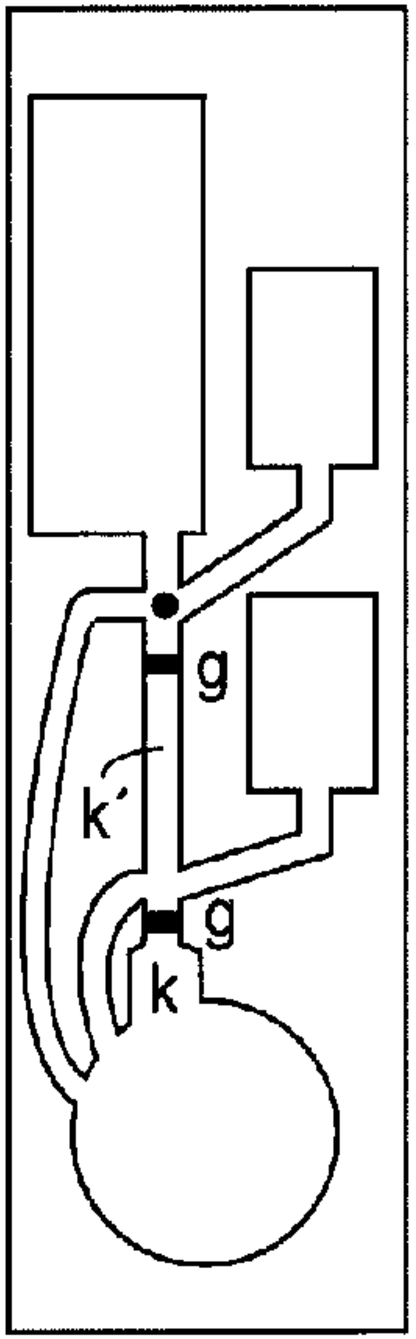
Fig.4



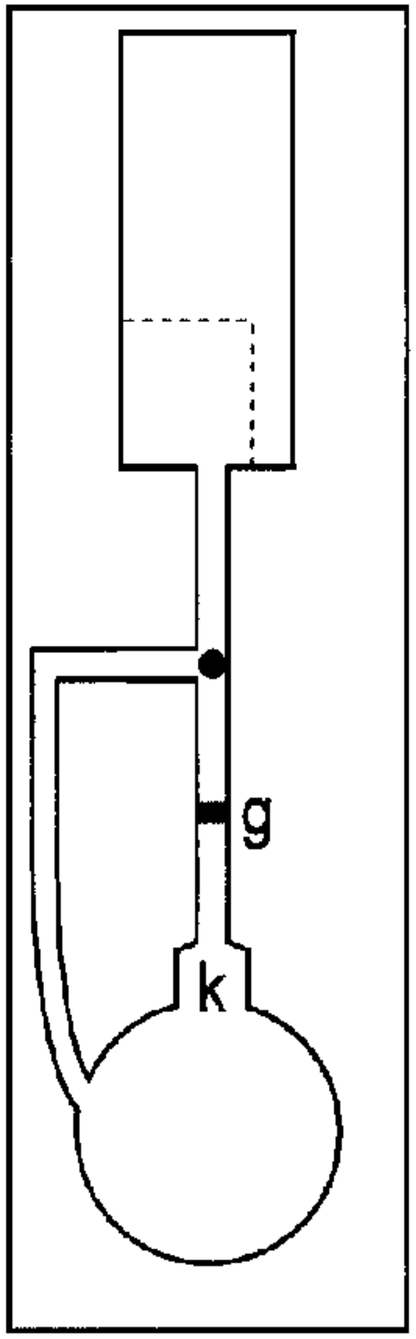
a



b



c



d