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(12) PATENT ABSTRACT (11) Document No. AU-A-20429/95
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- (54) Title
MAGNETIC MATERIAL ATTRACTING/RELEASING CONTROL METHOD MAKING USE OF A
PIPETTE DEVICE AND VARIOUS TYPES OF CLINICAL INSPECTION APPARATUS USING THE
METHOD
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- (57) Claim

1. A magnetic material attracting/releasing control method making use of a pipette device with a magnet body or magnet bodies provided in a liquid suction line of said pipette device for sucking a liquid from a container and discharging said liquid, said pipette device providing controls by absorbing and maintaining magnetic material contained in a liquid and attracted to a liquid suction line due to magnetism in said magnet body or bodies on an internal surface of said liquid suction line and also by releasing said magnetic material from said liquid suction line by means of interrupting effect by magnetism in said magnet body or bodies so that said magnetic material is discharged together with said liquid to outside of said liquid suction line.

ABSTRACT OF DISCLOSURE

A magnetic material attracting/releasing control method makes use of a pipette device sucking a liquid from or discharging a liquid into a container. A magnet body or bodies are provided in a liquid suction line of the pipette device, and any magnetic material contained in liquid sucked into the liquid suction line by magnetic force are deposited on the internal surface of the line. The magnetic material is released and discharged together with liquid from the liquid suction line to a state where the effect of the magnetic force generated by the magnet body is cut off.



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COMPLETE SPECIFICATION

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INVENTION TITLE:

Magnetic material attracting/releasing control method ~~making use of a pipette device and various types of clinical inspection apparatus using the method~~
and apparatus making use of a pipette device.

The following statement is a full description of this invention, including the best method of performing it known to me/us:-



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FIELD OF THE INVENTION

The present invention relates to a method and apparatus for attracting/releasing magnetic material suspended in a liquid.

5 It should be noted that, the "magnetic material", indicates not only ball-like materials, but also granular and corpuscular materials, and the form is not limited to a sphere; any form is allowable.

10 BACKGROUND OF THE INVENTION

In recent years, a variety of chemiluminescence methods (CL method) have been developed, which include, for instance, an enzyme immunoassay (EIA) that utilizes an antigen-antibody
15 reaction, a chemiluminescence immunoassay (CLIA) in a narrow sense in which a chemical illuminescent compound is used for labeling as a tracer for immunoassay, and a chemiluminescent enzyme immunoassay (CLEIA) which detects enzyme activity with high sensitivity by using a chemical luminescent compound in a
20 detection system.

As an inspection method using any of the techniques as described above, there have been known the magnetic particle method using magnetic particles each having a surface coated with an antigen or an antibody, the latex method using latex
25 having a surface coated with an antigen or an antibody, the beads method using spheric beads each having a surface coated with an antigen or an antibody, or the so-called tube coating



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method using cells each having an inner wall coated with an antigen or an antibody. When taking into account the efficiency of capturing an antigen or an antibody as well as production costs and running costs, methods using magnetic bodies such as 5 magnetic particles or beads are far more advantageous.

In the conventional type of inspection methods using a magnetic material as described above, it is required to clean the magnetic material or have the magnetic material reacted to a reagent by gathering the magnetic material floating or 10 depositing in a reactor, such as a specimen reaction container, or generating a floating state thereof several times in the reactor, however, it is extremely difficult to maintain high precision of gathering or agitating the magnetic material in the process, and this is one of the reasons why the inspection 15 method making use of magnetic material has not been automated for various applications.



Description is made of a flow in an immuno chemical process making use of a magnetic material as described above with reference to Fig. 9. In this flow, at first when a required quantity of specimen is
5 sampled in a container 1 with a first pipette device P_1 in step (a), a reaction insoluble magnetic liquid 3 is poured into the container 1 by a second pipette device P_2 in step (b). Agitation by a vibrating agitator is executed in step (c), incubation (under a constant
10 temperature) is executed in step (d), and attraction of magnetic material by a magnet M and discharge of the liquid are executed in step (e). A cleaning liquid is then poured by a third pipette device P_3 into the container in step (f).

15 Then in step (g), agitation is carried out by an shaking agitator, in step (h), the magnetic material 2 is attracted by the magnet M with the cleaning liquid discharged, in step labeling liquid 6 is poured in through a fourth pipette device P_4 , in step (j)
20 agitation is carried out by a shaking agitator, in step (k) incubation (reason under a constant reaction) is carried out, then in step (l) the magnetic material is attracted by the magnet M with the reaction liquid discharged, in step (m) the cleaning liquid is poured
25 in through a fifth pipette device P_5 . Then, in step (n), agitation is carried out by the shaking agitator.

Then, for instance, in CLEIA method, in step (o) the magnetic material 2 is attracted by the magnet

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M with the cleaning liquid discharged, in step (p) the carried liquid is poured in, in step (q) agitation is carried out by a shaking agitator, and then in step (r) the sample is left for a certain period of time, and in step (s) the quantity of light 5 emitted from the reaction system is measured with an optical measuring instrument such as PMT.

On the other hand, with the CLEIA method, after step (n) described above, in step (t) a cleaning liquid containing the magnetic material 2 in the vessel 1 is sucked out with the 10 cleaning liquid and poured into a measuring cell with a filter provided thereon, and the magnetic material 2 contained in the cleaning liquid is collected by the filter. Then, in step (u), hydrogen peroxide liquid (H_2O_2) is poured into the magnetic material 2 collected by said filter to have light emitted 15 transitionally, and a quantity of emitted light is measured by PMT tightly protected against light coming from outside.

On the other hand, in a checking method, like the CLEIA method or EIA method, in which light emission is continued for a certain period of time after a substrate liquid is poured in 20 step (s), in step (t) a quantity of light generated in the reaction is measured with an optical measurement instrument such as a PMT.

The above description relates to the conventional type of inspection method using a magnetic



material, but as clearly understood from the foregoing, in the conventional inspection method making use of the type of magnetic material as described above, it is required to attract the magnetic material onto the internal wall of a container and then homogeneously diffuse the attracted magnetic material into a liquid several times. It is extremely difficult to execute separation of the magnetic material from a liquid, agitation, and cleaning the container at high precision, a problem to be solved.

Namely, when separating the magnetic material from a liquid, in the conventional type of inspection method, generally magnetic attraction is produced on a side wall of a large container, requiring a long time to attract any magnetic material diffused in a liquid onto the internal wall of the container. Efficiency in gathering the magnetic material thus is disadvantageously very low.

Also, when gathering magnetic material on the internal surface of a container and inserting a pipette into a liquid to absorb the liquid, the magnetic material may be absorbed together with the liquid, and it is extremely difficult to completely capture the magnetic material.

Furthermore, when agitating the liquid with magnetic material diffused therein, generally to eliminate magnetism in a magnet and mix and diffuse the magnetic material once absorbed in liquid in the

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container, vibration is usually employed. However, it is difficult to diffuse the magnetic material in the liquid homogeneously, and the liquid containing the magnetic material mixed therein sometimes splashes out onto an upper surface of 5 the container, another problem to be solved. As a result, with vibration as employed in the conventional technology, the liquid containing magnetic material which has splashed out onto the upper surface of the container must be washed off. Hence, processing becomes more complicated, and if this operation for 10 washing off the liquid is carried out incompletely, the subsequent steps in the process are seriously affected.

Furthermore, when cleaning the liquid and magnetic material in the container as described above, materials other than those deposited on the surface of the magnetic material are removed by 15 carrying out processes for separating as well as agitating as described above, but the same problems as those that arise in separating and agitating may occur.

Also, in the inspection method making use of the conventional type of magnetic material, if a reaction process or 20 a treatment process is a very specific one, it is required to build mechanisms for separation, agitation, and cleaning as well as a control system suited to the specific process. Hence, the mechanisms or the control system become very complicated, and it is practically impossible to carry out an inspection making use 25 of a magnetic material based on a very specific reaction or treatment process. As a result, the facility or the operating cost becomes very high.

In addition, in the method of gathering magnetic material



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based on the aforementioned conventional technology, it is difficult to position the magnet as described above in such a container as, for instance, a microplate, and even if possible, it is difficult to position a magnet on a side face of the container. It is also difficult to carry out separation by attracting the magnetic material from a liquid, agitation and cleaning, and as a result it is extremely difficult to downsize the container by using a microplate, a serious disadvantage.

10 SUMMARY OF THE INVENTION

It is an object of the present invention to provide an improved method and apparatus for separation making use of an improved pipette, or to at least provide a useful alternative.

15 The pipette can realize substantial improvements in the measurement precision of an inspection method making use of magnetic material by complete attraction in a short period with a magnet provided on the pipette device. Cross-contamination is prevented if a disposable pipette chip or jet is used, and the

20 method can easily be applied to various types of inspection each based on a specific reaction or treatment process.

The present invention provides a method of attracting and releasing magnetic material suspended in a liquid using pipette means in a suction line, the pipette means having a thinnest tip

25 end portion, a large diameter reservoir and an intermediate diameter section therebetween, and one or more magnet bodies being detachably fitted to an external peripheral surface of the intermediate diameter section of the suction line, said method comprising the steps of:

30 aspirating the liquid containing the suspended material through the intermediate diameter section into the reservoir so that a lower end of a liquid level comes near to or higher than the lower end of said one or more magnet bodies,

applying a magnetic field to said intermediate diameter

35 section during a discharge of the liquid to separate said magnetic material from said liquid and



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to hold it on an internal surface wall of the intermediate diameter section, and

releasing the magnetic material by interrupting the magnetic field to discharge the magnetic material together with
5 the liquid from the pipette means.

The present invention also provides an apparatus for attracting and releasing magnetic material suspended in a liquid comprising pipette means in a suction line having a thinnest tip
10 end portion, a large diameter reservoir and an intermediate diameter section therebetween, and a magnet for controllably applying a magnetic field to said intermediate diameter section, said magnetic field being adapted to separate said magnetic material from said liquid during a discharge of the liquid and
15 to hold it on an internal surface wall of said intermediate diameter section and to release the magnetic material from the internal surface wall during a later discharge, the suction line being provided for controllably aspirating or discharging said liquid through said intermediate diameter section into said
20 reservoir and from said reservoir, respectively.

To enhance processing capability, a plurality of liquid suction lines are preferably provided in parallel to each other.

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Aspirating or discharging a liquid in each liquid suction line is driven and controlled. This enables realization of a multi-channel system allowing concurrent processing of a plurality of specimens.

5 Furthermore, to enhance the processing capability and respond to any liquid requiring a specific treatment process, it is preferred to provide a plurality of liquid suction lines described above. Each liquid suction line is controlled independently at a different timing so that suction and
10 discharge of liquid are controlled to attract or disperse the magnetic material for a specific treatment process.

At least one liquid suction line as described above is required. Improvement in processing capability can be achieved by integrating a liquid suction line and magnetic material into
15 a unit and providing a plurality of units as described above along a container transfer line.

The magnet may include any type of permanent magnet or electric magnet as far as it can generate magnetism for attracting a magnetic material. One or more pieces of magnet can
20 be provided in each liquid suction line in correspondence to the diameter of the liquid suction line, quantity of magnetic material to be attracted, and size thereof. Various arrangements for locating the magnets can be considered, for instance, magnets may be located in the direction in which a liquid flows
25 in the liquid suction line or at opposite positions in both sides of the liquid suction line, or in the radial direction.

Furthermore, the magnets can be displaced from the outside of the liquid suction line, or directly on the liquid suction



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line.

When locating magnets outside the liquid suction line as described above, by using a plurality pieces of permanent magnet and locating the magnet bodies on or near the liquid suction line, it is possible to absorb and maintain magnetic material contained in liquid attracted to the liquid suction line onto the internal surface of the liquid suction line. It is further possible to discharge the magnetic material together with the liquid from the liquid suction line by moving the magnetic bodies away from the liquid suction line to separate the magnetic material from the line.

When directly locating the magnet bodies on or near the liquid suction line, by forming the magnet bodies with electro-magnets and generating magnetism in the electro-magnets, it is possible to attract and maintain magnetic material contained in liquid aspirated into the liquid suction line on an internal surface of the liquid suction line. It is also possible to release the magnetic material from the liquid suction line by providing controls over the electro-magnets so that the magnetism is turned off or reduced when discharging the magnetic material together with the liquid from the liquid suction line. To form the electro-magnet as described above, an exciting coil may directly be attached to the liquid suction line itself or the coil may be wound around the liquid suction line. A configuration is also allowable in which the electro-magnet can be moved closer to or away from the liquid suction line.

The liquid suction line is preferably performed by dismountable mounting a pipette chip onto a tip section of the



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liquid sucking side thereof. The magnet body is arranged so that magnetism generated by the magnet body acts on the magnetic material inside the pipette chip.

Thus by making it possible, when aspirating or discharging
5 a liquid containing magnetic material with a pipette chip, to retain the magnetic material obtained in the liquid onto an internal surface of the pipette chip, the magnetic material can be captured as completely as possible. It is also possible to transfer a pipette chip with magnetic material deposited on an
10 internal surface to a next reaction or treatment step.

The pipette chip described above is used repeatedly only for the same specimen in a specified processing sequence for inspection to prevent cross-contamination. Any number of pipette chips may be used for the same specimen depending on the
15 requirements for a reaction or a treatment process in various types of inspection.

Separation of the magnetic material from the liquid, agitation and cleaning can be carried out by aspirating liquid into and discharging liquid from the liquid suction line once or
20 more than once.

Separation of magnetic material from a liquid is executed by maintaining the state where magnetic material is absorbed and deposited on the internal surface of a liquid suction line and discharging only the liquid. This is alternatively accomplished
25 by inserting a pipette chip with magnetic material attracted and deposited on an internal surface thereof into liquid stored in another container and repetitiously aspirating and discharging the liquid.



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Thus, by executing separation of the liquid and magnetic material by means of repetitiously aspirating and discharging the liquid in a pipette device, it is possible to almost completely capture the magnetic material. The almost complete
5 separation of magnetic material from the liquid can be realized in all processes requiring separation of magnetic material from a liquid containing it.

When a pipette chip is mounted on a liquid suction line, the agitation and cleaning steps described above are executed by
10 transferring the pipette chip with magnetic material attracted by the magnet body and deposited onto an internal surface thereof to the position for agitation and cleaning and then repeating the operations for aspirating and discharging the liquid.

15 As described above, it is possible to homogeneously diffuse magnetic material in a liquid. It is also possible to improve the cleaning efficiency, and in addition, although the aspirating and discharging is executed between the liquid suction line and the container, the liquid does not splash out
20 from the container. Hence, the agitation and cleaning processes can be executed under stable conditions without lowering precision in measurement due to the possible splashing of the liquid containing magnetic material.

The operations for separating magnetic material from a
25 liquid, agitation and cleaning can be executed by transferring a magnet body to a liquid containing magnetic material previously stored in a liquid storage section in a cartridge having a plurality of liquid storage sections therein.



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Aspiration or discharging of the liquid is performed according to need, or by maintaining the state where magnetic material is deposited on an internal surface of a pipette chip and discharging the residual liquid from the container. Then, liquid
5 required for the next process is poured into the same container and sucking or discharging the liquid poured anew is carried out with the pipette chip. No specific form of container is required for aspirating and discharging the liquid in a liquid suction line to execute the separation operations, agitation, and
10 cleaning.

It is also possible to execute both qualitative and quantative assessment of a target substance contained in a liquid by accurately controlling the quantity of liquid sucked by a liquid suction line.

15 The method according to the present invention is applicable to and effective in inspection procedures based on reactions generated between a target substance present in a liquid and other materials which can be physically and/or chemically deposited on the magnet body. The substances materials include
20 immunological materials, biological materials, and molecular-biological materials such as antigens, antibodies, proteins, enzymes, DNA, vector DNAs, RNAs or plasmid. The method can be applied to inspection or analysis of isotopes required for
qualitative or quantative analysis, enzymes, and other labeling
25 materials used for chemiluminescence, fluoro-illuminescence, and electro-chemical illuminescence. For instance, the method can be applied to an apparatus for immunological assay or inspections making use of chemical reaction, extraction, recovery or



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separation of DNAs.

When the method is applied to an immunochemical inspection apparatus, a container is formed in a cassette having a plurality of liquid storage sections. A liquid or reagent 5 required for reaction or processing is poured into each liquid storage section, and the container should preferably be transferred with a magnetic material attracted by the magnet body to and deposited on an internal surface of a liquid suction line as is. In this case, the liquid is previously poured into 10 each liquid storage section as described above, and only a portion thereof may be processed or be processed gradually in the treatment process.

Furthermore, a specimen can directly be measured quantitatively, for instance, in a parent specimen container and 15 then poured into each liquid storage section. It should be noted that the liquid storage sections in the cassette may be arranged either in a single array or in a plurality of arrays and formed into a form like a microplate. If the cassette is a form like a microplate, a multi-channel system can be realized by locating 20 a plurality of liquid suction lines in correspondence to the liquid storage section arrays, and thus the processing capability is substantially improved.

Other features of this invention will become understood from the following description, by way of example only, with 25 reference to the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a flow chart showing processes in a case where



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the present invention is applied to an immunochemical inspection method based on the chemiluminescence method;

Fig. 2 is a cross-sectional view showing an example of a pipette chip;

5 Fig. 3 is an explanatory view showing an example of the general configuration of a measurement section for an immunochemical inspection method based on the CLEIA method;

Fig. 4 is an explanatory view showing the general configuration of a measurement section for an immunochemical inspection method based on the CLIA method;

Fig. 5 is an explanatory view showing the general configuration of a measurement section for an immunochemical inspection method based on the EIA method;

Fig. 6 is an explanatory view showing an example of the arrangement of a magnet in an embodiment including a nozzle system;

Fig. 7 is an explanatory view showing another example of an arrangement of the magnet;

Fig. 8 is an explanatory view showing still another example of an arrangement of the magnet; and

Fig. 9 is a flow chart showing processes in an immunochemical inspection method based on the conventional type of chemiluminescence method.

25 DESCRIPTION OF THE PREFERRED EMBODIMENTS

Detailed description is made for an embodiment of an immunochemical inspection method based on the chemiluminescence



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method. As described above, the field of application of the present invention is not limited to this embodiment.

A flow of an immunochemical inspection according to an embodiment of the present invention as compared to a flow of the 5 conventional type of immunochemical inspection is described below with reference to Fig. 1.

It should be noted that, in this embodiment, the magnetic material is defined as magnetic material, which can be adhered at its surface with an antigen or an antibody. The magnetic 10 material is attracted by a magnet for B/F separation (separation of materials bound to antigen or antibody and those not bound to them).

In this figure, the sign P indicates a pipette chip or jet for pouring a specified quantity of specimen from a parent 15 vessel, such as a blood tube (not shown), into a specimen reaction container 1 and also for removing from or supplying to the specimen reaction container 1 a reaction insoluble magnetic material liquid 3, a cleaning liquid 5, an enzyme-labeling liquid 6, a substrate liquid 7, a reaction stop liquid or the 20 like.

As shown in Fig. 2, the pipette chip P has a three-staged form consisting of a thinnest section 10 inserted into the specimen reaction container 1, a medium diameter section 11 having a larger diameter than the thinnest section 10, and a 25 large diameter section 12 having a larger diameter than the medium diameter section 11. A magnet M for attracting the reaction insoluble magnetic material 3 is detachable fitted to an external peripheral surface of the medium diameter section 11



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with a mechanism for aspirating or discharging liquid in a cylinder disconnectable connected and communicated to a top edge section of this pipette chip P. It is needless to say that the form of this pipette chip P is not limited to that shown in 5 this figure. To completely capture the magnetic material with the magnet, however, it is desirable to form the intermediate section contacted by the magnet with a small diameter. This also is preferable for efficiently controlling flow rate while sucking or discharging liquid.

10 It should be noted that, when extracting, recovering, or separating DNA material, a molded pipette chip having a large diameter may be used to prevent the DNA material from being damaged due to the physical force effecting magnetic material deposited on the DNA material and generated when liquid is 15 aspirated or discharged.

In the specimen reaction container 1, a plurality of liquid storage sections 1A through 1H are provided in a straight array, in a loop, or in a zig-zag form with a roughly specified quantity of specimen having been poured in the liquid storage 20 section 1A, a specified quantity of reaction insoluble magnetic



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material liquid 3 in the liquid storage section 1B, a specified quantity of cleaning liquid 5 in the liquid storage sections 1C and 1D, a specified quantity of labeling liquid in the liquid storage section 1E, a specified quantity of cleaning liquid 5 in the liquid storage sections 1F and 1G, each filled with the liquid before start of inspection, and a substrate liquid in the liquid storage section 1H for measurement of the light-emitting state.

10 In the case of the CLIA or CLEIA inspection, the specimen reaction container 1 is made of opaque material to prevent any effect by luminescence, and in the case of the EIA inspection at least the bottom section is made of a transparent material.

15 When carrying out immunochemical inspection according to the present invention using the specimen reaction container 1 constructed as described above and the pipette chip P, the specimen having been poured into the liquid storage section 1A by a roughly specified quantity is sucked with the pipette chip P above by a specified quantity for quantitative analysis.

20 Then, the pipette chip P with the specimen sucked therein is transferred and all of the specimen having been sucked is discharged into the reaction insoluble magnetic material liquid 3 in the liquid storage section 1B. A mixture of the specimen and the reaction insoluble magnetic material liquid 3 then is

repeatedly sucked and discharged with the pipette chip P (this operation is called liquid sucking/discharge hereinafter) to generate a state where the magnetic material 2 has been homogeneously agitated and mixed therein. In several hours, all, or a specified quantity of, the incubated mixed liquid is sucked with the pipette chip P.

In this step, the magnetic material 2 floating in the mixed liquid sucked by the pipette chip P is captured onto an internal wall surface of the medium diameter section 11 due to magnetism of the magnet M provided outside the pipette chip P, as shown in Fig. 2, when the mixed liquid passes through the medium diameter section 11 of the pipette chip P. The mixed liquid is sucked into the pipette chip P to the height shown in Fig. 2, so that, when all the mixed liquid is sucked into the pipette chip, the bottom face x comes near a lower edge of the magnet M or to a level higher than that and the magnetic material 2 is completely captured.

After all the magnetic material 2 has been captured, the mixed liquid with the magnetic material having been removed therefrom is discharged into the liquid storage section 1B, and only the magnetic material 2 remains in the pipette chip P. As the magnetic material 2 is wet then, even if the mixed liquid is exhausted, the magnetic material 2 is kept deposited on an internal surface of the medium diameter

section 11 of the pipette chip P, so that, even if the pipette chip is transferred, the magnetic material rarely drops off from the internal surface. Then the pipette chip P is transferred to the next liquid storage section 1C with the magnetic material 2 captured therein, and sucks the cleaning liquid 5 in the liquid storage section 1C. Then the magnet M moves away from the pipette chip P to release the magnetic material 2, and therefore by sucking and discharging the cleaning liquid 5, all the magnetic material 2 can efficiently be cleaned.

After the operations for sucking and discharging the liquid are finished, the pipette chip P slowly sucks all the cleaning liquid 5 (for 5 to 10 seconds) in the liquid storage section 1C. Then the magnet M is again moved toward the pipette chip P to capture all the magnetic material 2 floating in the sucked cleaning liquid 5, and the cleaning liquid 5 with the magnetic material 2 having been removed therefrom is discharged into the liquid storage section 1C, so that only the magnetic material 2 remains in the pipette chip P.

Then the pipette chip P is transferred to the next liquid storage section 1D with the magnetic material 2 captured therein and sucks the cleaning liquid 5 in the liquid storage section 1D, where the operations for cleaning and capturing the magnetic material 2 are executed according to the same sequence

as that in the liquid storage section 1C.

Then the pipette chip P is transferred to the next storage section 1E with the cleaned magnetic material 2 captured therein, and sucks the labeling liquid 6 in the liquid storage section 1E. Then the magnet M moves away from the pipette chip P to release the magnetic material 2, and thus by sucking and discharging the labeling liquid 6, all the magnetic material 2 and the labeling liquid 6 can be reacted to each other homogeneously.

After the operations for sucking and discharging the liquid are finished, incubation is continued for a specified period of time, and then the pipette chip P slowly sucks all the labeling liquid 6 in the liquid storage section 1E (for instance, for 5 to 10 seconds). Then the magnet M again goes near the pipette chip P to capture all the magnetic material 2 floating in the sucked labeling liquid 6, and the labeling liquid 6 with the magnetic material 2 having been removed therefrom is discharged into the liquid storage section 1E, and only the magnetic material 2 remains in the pipette chip P.

Then the pipette chip P is transferred to the next liquid storage section 1F with the magnetic material 2 captured therein, sucks the cleaning liquid 5 in the liquid storage section 1F, executes operations for cleaning and capturing the magnetic material 2 according to the same sequence as those in the liquid

storage sections 1C and 1D, sucks the cleaning liquid
5 in the liquid storage section 1G according to the
same sequence as that for sucking the cleaning liquid
in the liquid storage section 1F, and then executes
5 operations for cleaning and capturing the magnetic
material 2.

Then the pipette chip P is transferred to the
liquid storage section 1H, and for instance if a
measurement in which illuminescence is continued after
10 mixed with a substrate liquid and a certain period of
time is required until a rate of light emission is
stabilized as in the CLEIA inspection is to be carried
out, the substrate liquid 7 previously stored in the
liquid storage section 1H is sucked by the pipette chip
15 P. Then the magnet M moves away from the pipette chip
P and releases the magnetic material 2, so that it is
possible to homogenize the reaction between the
magnetic material 2 and the substrate liquid 7 by
sucking and discharging the substrate liquid 7.

20 When the operations for sucking and
discharging the liquid have been finished and
incubation has been executed for a certain period of
time, a quantity of emitted light is measured by the
optical measurement instrument 9 such as a PMT as shown
25 in Fig. 3.

In the case of an inspection method in which
illuminescence is continued only for a very short
period of time as in CLIA inspection, the liquid

storage section 1H is provided as shown in Fig. 4, a filter 16 and a water-absorbing pad 20 is provided in the liquid storage section 1H, and the magnetic material 2 is discharged together with the cleaning liquid 5 sucked in the previous process from the pipette chip P into the liquid storage section 1H to have the magnetic material 2 captured by the filter 16. Then a light-emitting trigger liquid 7 such as hydrogen peroxide liquid (H_2O_2) is supplied from a nozzle 17 to make the magnetic material emit light, and a quantity of light emitted when said substrate liquid is poured may be measured with an optical measurement instrument 9 such as a PMT.

Furthermore, in the case of EIA inspection, after the substrate liquid 7 is poured, a reaction stop liquid is supplied and as shown in Fig. 5, a light beam having a specified wavelength is irradiated from a bottom section of the liquid storage section 1H, and a degree of absorbency is measured by a light-receiving element and a detector by checking the specific color.

Thus, with the specimen reaction container 1 according to the present embodiment, it is possible to respond to a plurality types of immunochemical inspection by changing only configuration of the liquid storage section 1H in correspondence to various inspection methods, so that the versatility can substantially be improved. Also a multi-channel system of this type can be realized by providing liquid

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storage section in a plurality of arrays in the specimen reaction container 1 to form it into a form like a microplate.

Then the pipette chip P and the specimen reaction container 1 are disposed.

5 It should be noted that, although the description of the embodiment above assumed a case in which the specimen reaction container 1 is cleaned twice after the reaction insoluble magnetic material liquid 3 is discharged and furthermore 2 times after the labeling liquid 6 is discharged, the present invention
10 is not limited to the configuration described above: the specimen reaction container 1 may be cleaned any number of times according to need.

Also the above description assumes the configuration in which the pipette chip P is transferred to each liquid storage
15 section in the specimen reaction container 1, but a configuration is allowable in which the pipette chip P is moved only in the vertical direction and the specimen reaction container 1 is intermittently transferred for executing each of the operations described above.

20 Furthermore, the description of the above embodiment assumed a case where the pipette chip P and the specimen reaction container 1 are disposable, although a configuration is allowable where the pipette chip P and the specimen reaction container 1 can be cleaned and used repeatedly. Also, the
25 description of



the above embodiment assumed a case in which the waste liquid after being sucked by the pipette chip P is recycled to the original liquid storage section from which the liquid was sucked. A configuration is also
5 allowable, however, where the waste liquid is returned to a waste liquid section provided outside the specimen reaction container 1.

It is needless to say that the present invention is applicable to a case where the pipette
10 chip P is not used and a liquid suction line is formed as a nozzle system, and in this case, the configuration as shown in Fig. 6 is allowable where a lower edge section P_A of the liquid suction line P_1 is formed into a thin diameter section, and the magnet M or an
15 electro-magnet is moved to or away from the lower edge section P_A of the liquid suction line P_1 . When using the electro-magnet, a configuration is allowable where the electro-magnet is fitted to the thin diameter section of a liquid suction line or the electro-magnet
20 is directly wound around the thin diameter section of the liquid suction line and operations for separating magnetic material from a liquid, agitation, and cleaning are executed by turning ON or OFF a current.

Also, the description of the embodiment above
25 assumes a case where the magnet M is detachably fitted to one side of the medium diameter section 11 of the pipette chip P, but the magnets M may be provided in both sides of the medium diameter section 11 as shown

in Fig. 7. Also, a plurality of magnets M may be provided in a radial form around the medium diameter section 11 shown in Fig. 8, and also a plurality of magnets may be provided along the longitudinal
5 direction of the medium diameter section 11, although that case is not shown herein.

As described above, in the present invention, magnetic material is loaded or unloaded by making use of a pipette device, and capture of the magnetic
10 material is executed not in the side of a container in which a liquid is stored, but in the side of a liquid suction line for sucking and discharging a liquid containing magnetic material by making use of magnetism in a magnet provided therein, so that the magnetic
15 material can almost completely be captured within a short period of time.

Also, in the present invention, a multi-channel system in which a plurality of specimens can be processed concurrently and the processing capability
20 can be enhanced by providing a plurality of the liquid suction line described above and controlling the operations for sucking and discharging a liquid so that each liquid suction line absorbs or releases magnetic material at the same timing respectively.

25 Furthermore, in the present invention, processing can be enhanced and various types of liquid each requiring a specific process can be processed by providing a plurality of liquid suction lines described

above and controlling each of the liquid suction lines
so that magnetic material is absorbed or released by
sucking or discharging each liquid containing the
magnetic material independently at a different timing
5 according to a specified process required for each
liquid.

The processing capability can be furthermore
enhanced by integrating a liquid suction line and a
magnet body into a unit and providing a plurality of
10 units along the container transfer line.

In the present invention, when a liquid
containing magnetic material is sucked or discharged,
the magnet material is absorbed onto an internal
surface of the pipette chip, so that the magnetic
15 material can almost completely be captured, and the
pipette chip can be transferred to the next reaction
process or processing step with the magnetic material
deposited on the internal surface thereof.

The pipette chip is repeatedly used only for
20 the same specimen in a process in which a specimen is
processed according to a specified inspection method,
so that cross contamination can be prevented. If the
liquid suction line is based on a nozzle system in
which a pipette chip is not loaded or unloaded, it is
25 possible to prevent cross contamination by cleaning an
internal surface of the liquid suction line by means of
sucking and discharging a liquid.

Furthermore, in the present invention,

operations for separating magnetic material from a liquid containing the magnetic material therein, agitation and cleaning are executed by sucking and discharging the liquid with the cleaned liquid suction line described above once or more, so that the magnetic material can almost completely be captured. In addition, in the present invention, the operations of agitating and cleaning magnetic material are executed, as described above, in the side of a liquid suction line of a pipette device by sucking and discharging a liquid, so that the magnetic material can homogeneously be diffused in a liquid, and also the cleaning efficiency can be improved. In addition, although sucking and discharge of a liquid is executed between a liquid suction line and a container, the liquid containing magnetic material never splashes out. As a result, the operations of agitation and cleaning can be stabilized and precision in measurement does not become low due to contamination by the magnetic material containing liquid splashing out.

In the present invention, a quantity of liquid to be sucked can be controlled by the liquid suction line accurately, so that both qualitative and quantitative analysis of a target material contained in a liquid can be executed with high precision.

Furthermore, the method according to the present invention can be applied to various types of apparatus, and in this case a mechanism required for

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controlling magnetic material can substantially be simplified, and precision in measurement substantially improved and stabilized.

Although the invention has been described with respect to 5 a specific embodiment for a complete and clear disclosure, the appended claims are not to be thus limited but are to be construed as embodying all modifications and alternative constructions that may occur to one skilled in the art which fairly fall within the basic teaching herein set forth.

10 Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other 15 integer or step or group of integers or steps.



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in the treating liquid from the pipette means into a further container to analyse the target substance extracted with the magnetic material.

5 3. The method of claim 2, wherein the treating step (b) alternatively comprises repeatedly aspirating and discharging the suspended magnetic material to and from the pipette means without application of the magnetic field to thereby agitate the suspension.

10

4. The method of claim 2, wherein the treating step (b) comprises repeatedly aspirating and discharging a cleaning liquid to and from the pipette means while the magnetic material is held by the magnetic field to the internal surface wall, to
15 thereby effect a cleaning of the magnetic material.

5. The method of claim 2 or 3, wherein the transferring step (c) produces a test mixture, the method further comprising testing the test mixture to analyse, extract or recover the
20 target substance.

6. The method of claim 2, 3 or 4, wherein said step (a) comprises transferring a first predetermined amount of the suspension from a first vessel to the reservoir of the pipette
25 means.

7. The method of claim 6, wherein said step (a) further comprises discharging the first predetermined amount of the



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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of attracting and releasing magnetic material suspended in a liquid using pipette means in a suction line, the
5 pipette means having a thinnest tip end portion, a large diameter reservoir and an intermediate diameter section therebetween, and one or more magnet bodies being detachably fitted to an external peripheral surface of the intermediate diameter section of the suction line, said method comprising the
10 steps of:

aspirating the liquid containing the suspended material through the intermediate diameter section into the reservoir so that a lower end of a liquid level comes near to or higher than the lower end of said one or more magnet bodies,

15 applying a magnetic field to said intermediate diameter section during a discharge of the liquid to separate said magnetic material from said liquid and to hold it on an internal surface wall of the intermediate diameter section, and

releasing the magnetic material by interrupting the
20 magnetic field to discharge the magnetic material together with the liquid from the pipette means.

2. The method of claim 1 comprising the steps of:

(a) mixing a liquid specimen containing a target substance
25 with the magnetic material in a container to form said liquid suspension of the magnetic material;

(b) treating the magnetic material in the aspirated liquid, including the steps of applying the magnetic field and releasing the magnetic field to resuspend the magnetic material
30 into a further treating liquid;

(c) transferring the treated magnetic material contained



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liquid suspension from the pipette means to a second vessel comprising a second predetermined amount of the magnetic material.

5 8. The method of any one of claims 1 to 7 wherein the magnetic material comprises insoluble magnetic particles suspended in the liquid.

9. The method of any one of the claims 2 to 8 wherein said
10 step (c) further comprises repeatedly transferring the treated magnetic material in the treating liquid from the pipette means to the container and from the container to the pipette means to provide agitation until the magnetic material has homogeneously mixed with the treating liquid.

15

10. The method of any one of the claims 1 to 8 wherein the flow rate while aspirating and discharging the liquids is controlled.

11. The method of any one of the claims 2 to 9 wherein said
20 step (b) comprises transferring cleaning liquid as a treating liquid from a third vessel to the reservoir after discharging the present liquid.

12. The method of claim 11, wherein said step (b) further
25 comprises removing the magnetic field after the cleaning liquid is transferred to the reservoir.

13. The method of claim 11 or 12, wherein said step (b)

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comprises cleaning the magnetic material by transferring the cleaning liquid and the magnetic material from the reservoir to the third vessel and from the third vessel to the reservoir when the magnetic field is removed.

5

14. The method of claim 13 wherein the magnetic field is applied after the step of cleaning to accumulate the magnetic material on the inside wall of the intermediate diameter section and to discharge the cleaning liquid.

10

15. The method of any one of the claims 11 to 13 wherein said step of cleaning is repeated more than once.

16. The method of any one of the claims 11 to 15 wherein said
15 step (b) comprises transferring a labeling liquid from a fourth vessel to the reservoir after discharging the cleaning liquid.

17. The method of claim 16 wherein said step (b) further
20 comprises labeling the target substance by transferring the labeling liquid and the magnetic material from the reservoir to the fourth vessel and from the fourth vessel to the reservoir when the magnetic field is removed.

18. The method of claim 17 wherein the magnetic field is
25 applied after the step of labeling to accumulate the magnetic material on the inside wall of the reservoir and to discharge the labeling liquid.



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19. The method of any one of the claims 16 to 18 wherein the step of cleaning is repeated after the step of labeling.

20. The method of any one of the claims 2 to 16 wherein said 5 step (c) comprises transferring a substrate liquid from a fifth vessel to the reservoir when the magnetic field is applied.

21. The method of claim 20, wherein said step (c) comprises discharging the substrate liquid and the magnetic material from 10 the reservoir to the fifth vessel when the magnetic field is removed to produce a test mixture in the fifth vessel.

22. The method of claim 20 or 21 wherein the substrate liquid comprises light-emitting trigger liquid.

15

23. The method of any one of the claims 1 to 22 wherein a plurality of said liquid suction lines are provided in parallel to each other and said liquid suction lines are driven and controlled such that aspiration or discharge operations take 20 place concurrently in all lines at once or independently in each line.

24. The method of claim 23, wherein said liquid suction lines and magnet are integrated into a unit and a plurality of such 25 units are provided along a container transfer line.

25. The method of claim 24 wherein said magnet comprises a permanent magnet, said magnetic material contained in a liquid



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is attracted to and held on an internal surface of said pipette means when said magnet approaches said pipette means, and said magnetic material is discharged together with said liquid from said pipette means by separating said magnetic material from
5 said pipette means by retracting said magnet from said pipette means.

26. The method of claim 24, wherein said magnet comprises an electro-magnet, said magnetic material contained in a liquid is
10 attracted and maintained on an internal surface of said liquid suction line by applying a magnetic force with said electro-magnet, and said magnetic material is separated from said pipette means and discharged together with a liquid from said pipette means when fully reducing the magnetic force generated
15 by said electro-magnet.

27. The method of any one of the claims 23 to 26 wherein a pipette jet is releasably mounted onto an end section of said liquid suction line to form said pipette means and the magnetic
20 force generated by said magnet reaches the magnetic material in a liquid drawn into said pipette jet.

28. The method of claim 27, wherein said pipette jet is transferred to a specific processing position according to the
25 inspection method with magnetic material attached to and maintained on an internal surface thereof.



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29. The method of claim 27 or 28, wherein said pipette jet is repeatedly used only for the same specimen according to the specified inspection method required by the target substance.

5 30. The method of any one of the claims 23 to 29, wherein operations for separating said magnetic material from a liquid, agitation and cleaning are executed after inside and outside of a liquid-contacting section of said liquid suction line are cleaned by means of aspirating and discharging said liquid
10 repeatedly to a degree at which cross-contamination does not occur.

31. The method of any one of the claims 23 to 30 wherein separation of said magnetic material from a liquid, agitation
15 and cleaning are executed by once or more performing said operations for aspirating and discharging said liquid with said pipette means.

32. The method of claim 31 wherein said separation of magnetic
20 material from a liquid is executed by discharging only said liquid with said magnetic material kept attracted by said magnetic device.

33. The method of claim 30 wherein said agitation is executed,
25 after said pipette jet has been inserted into a liquid stored in the other container with magnetic material attracted on an internal surface of said pipette jet by said magnetic device by aspirating and discharging said liquid repeatedly in a state



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where said operations are not affected by a magnetic force generated by said magnetic device.

34. The method of claim 30 wherein said cleaning is executed, after said pipette jet is transferred to a cleaning position with said magnetic material attracted onto an internal surface of said pipette jet by said magnetic device, by aspirating and discharging said cleaning liquid repeatedly.

35. The method of claim 30, wherein said cleaning with a cleaning liquid is executed with magnetic material attracted onto an internal surface of said pipette jet.

36. The method of claim 30, wherein said cleaning with a cleaning liquid is executed by aspirating and discharging a cleaning liquid once or more in a stage where said operations are not affected by a magnetic force generated by said magnetic device.

37. The method of claim 30, wherein said separation of magnetic material from the liquid, agitation and cleaning are executed by aspirating and discharging a liquid previously stored in each of liquid storage sections provided in a cartridge with one or more liquid storage sections provided therein according to necessity.

25

38. The method of claim 30, wherein said separation of magnetic material from a liquid, agitation and cleaning are executed by discharging a residual liquid from said container with magnetic



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material deposited on an internal surface of said pipette jet, then poring a liquid required for the next processing into the same container and aspirating and discharging the poured liquid with said pipette jet.

5

39. Use of a method according to any one of the claims 1 to 38 in an inspection method wherein a substance is adhered to the magnetic material, wherein the substance includes immunological, biological or molecular-biological materials such as antigens, antibodies, proteins, enzymes DNA vector DNAs RNAs or plasmide, or the substance includes chemical compounds or enzymes for immuno-chemical assays based on chemiluminescence or electrochemical luminescence.

15 40. An apparatus for attracting and releasing magnetic material suspended in a liquid comprising pipette means in a suction line having a thinnest tip end portion, a large diameter reservoir and an intermediate diameter section therebetween, and a magnet for controllably applying a magnetic field to said intermediate
20 diameter section, said magnetic field being adapted to separate said magnetic material from said liquid during a discharge of the liquid and to hold it on an internal surface wall of said intermediate diameter section and to release the magnetic material from the internal surface wall during a later
25 discharge, the suction line being provided for controllably aspirating or discharging said liquid through said intermediate diameter section into said reservoir and from said reservoir, respectively.



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41. The apparatus of claim 40 wherein said thinnest tip portion is insertable into a storage section of a container.

42. The apparatus of claim 40, wherein said magnet comprises a permanent magnet being adapted to approach and retreat from said pipette means.

43. The apparatus of claim 40 wherein said magnet comprises an electromagnet for controllably generating said magnetic field.

10

44. The apparatus according to claim 40 to 43 wherein the pipette is dismountably mounted onto a tip section of said suction line.

15 45. The apparatus of claim 44, in which the pipette is a disposable item.

46. The apparatus according to claim 41, wherein a container is formed into a cassette-like form having a plurality of liquid storage sections, liquid and specimens are previously poured into each of said liquid storage sections according to the necessity in reaction or processing, and said container is transferred with said magnetic material deposited on an internal surface of a liquid suction line by a magnetic generated by said magnet.

20
25

47. The apparatus according to claim 41, wherein said container is formed into a form like a microplate having a plurality of



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liquid storage sections provided and arrayed therein.

48. A method of attracting and releasing magnetic material
suspended in a liquid substantially as hereinbefore described
5 with reference to the accompanying drawings.

49. An apparatus for attracting and releasing magnetic material
suspended in a liquid substantially as hereinbefore described
with reference to the accompanying drawings.

10

DATED this 10th day of February, 1999

15

PRECISION SYSTEM SCIENCE CO., LTD.

By its Patent Attorneys

20 DAVIES COLLISON CAVE



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FIG. 1

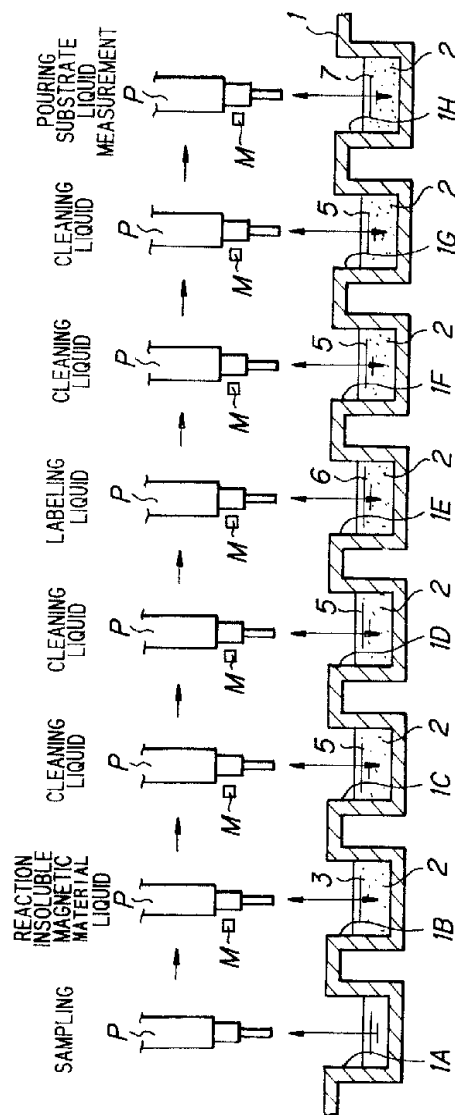


FIG. 2

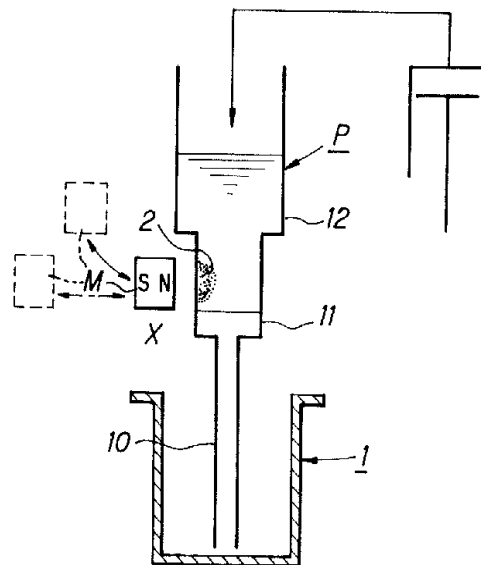


FIG. 3

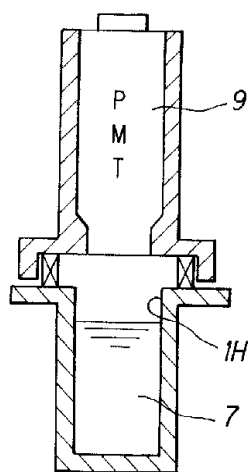


FIG. 4

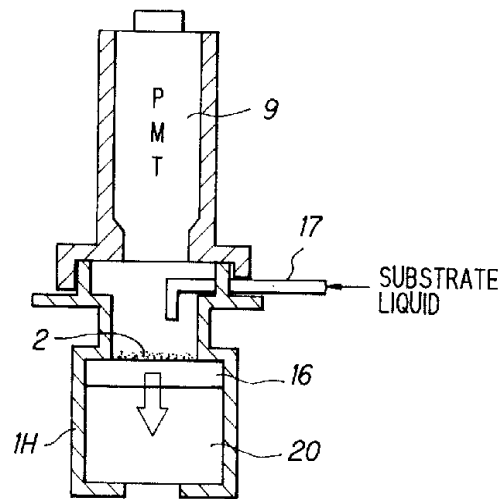


FIG. 5

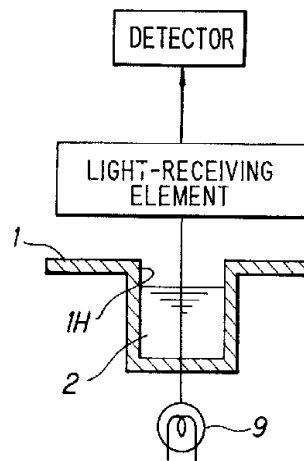


FIG. 6

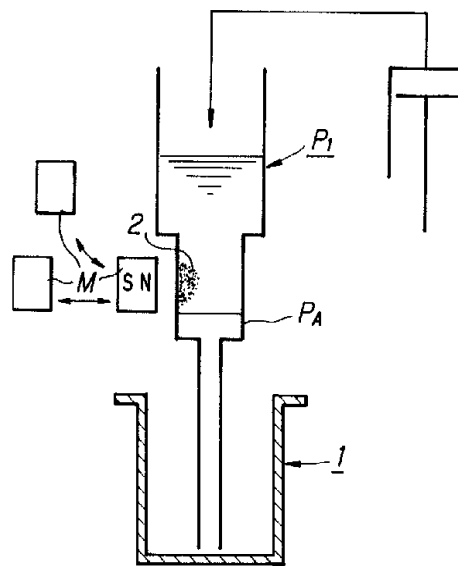


FIG. 7

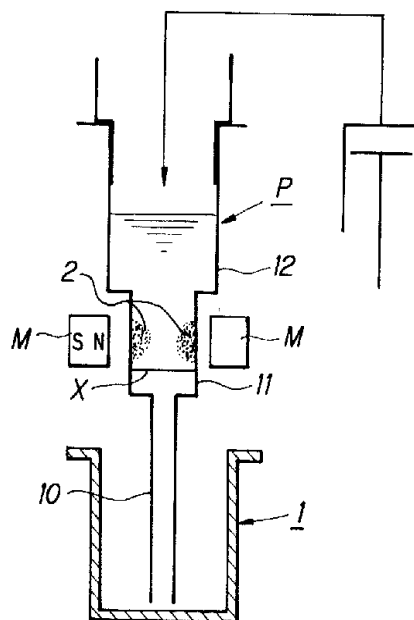
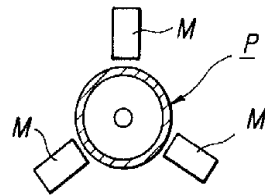


FIG. 8



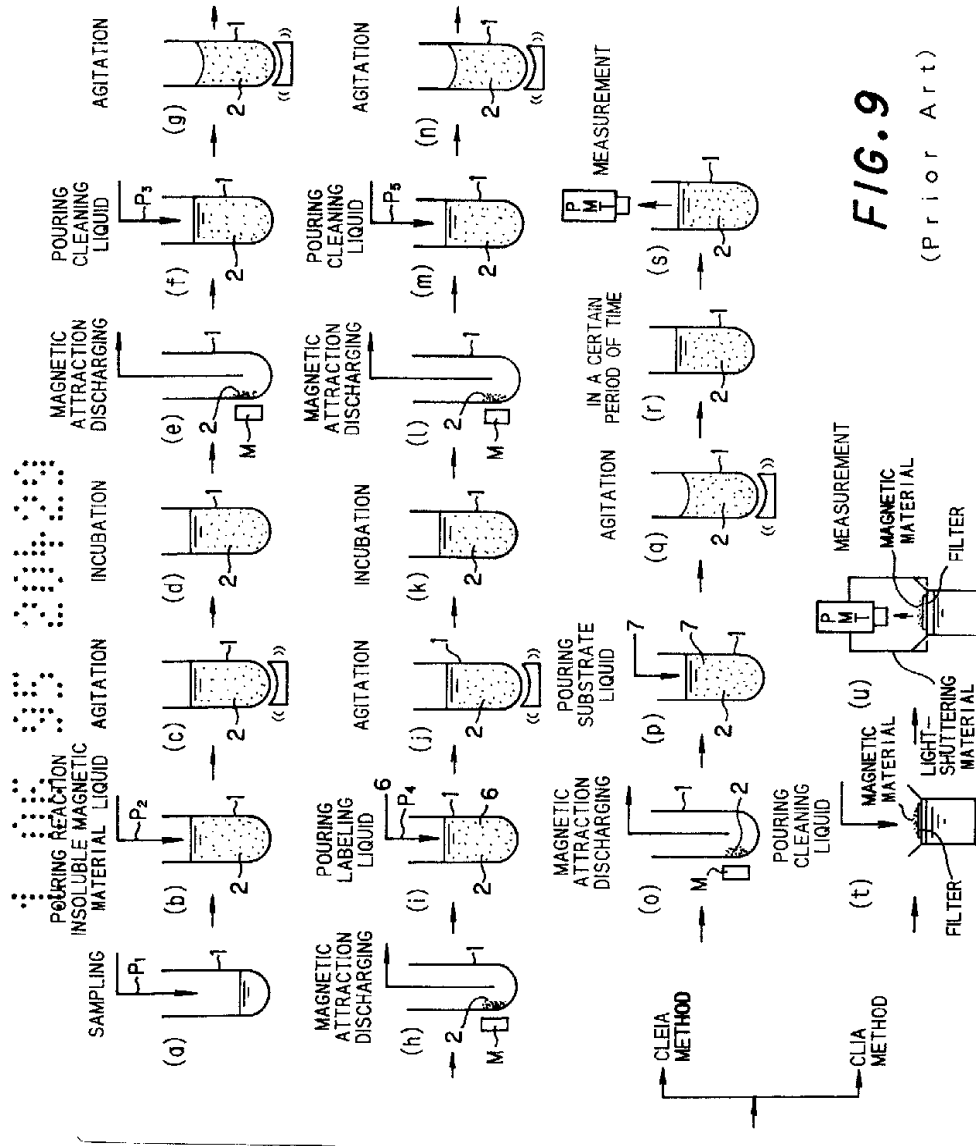


FIG. 9

(Prior Art)