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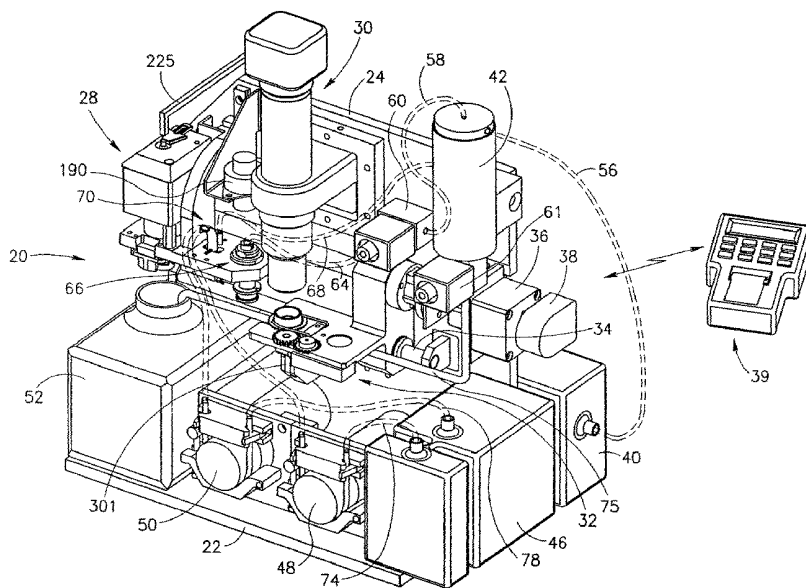
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(54) Title: APPARATUS AND METHOD FOR PROCESSING AND TESTING A BIOLOGICAL SPECIMEN



(57) Abstract: An apparatus for analyzing liquid specimens, the device comprising at least one specimen handling station for obtaining preparation on a specimen carrying device, and an imaging station fitted with an optical image capturing device for analyzing the preparation. A carriage with a specimen carrying device receptacle rotatably retains the specimen carrying device and is displaceable between a loading station and an unloading station with respective positions at the stations. An incremental displacement mechanism for displacing at least one of the specimen carrying device and an imaging device so as to obtain at least one consecutive image of the preparation.



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APPARATUS AND METHOD FOR PROCESSING AND TESTING A BIOLOGICAL SPECIMEN

FIELD OF THE INVENTION

The present invention relates to an apparatus and method for assaying specimens. In particular, the apparatus and method of the invention are suitable for testing techniques which involve an image analysis or assessment stage, e.g. the
5 method performed using an optical microscope.

BACKGROUND OF THE INVENTION

Assaying of biological specimens is routine laboratory procedure, both in clinical as well as in the research laboratory. Examples of specimens which are routinely tested consist of urine, blood and others. A critical blood parameter which
10 needs to be determined, primarily in hospital emergency rooms and intensive care units, as well as in patients prior to operation, concerns platelet function. U.S. Patent No. 5,523,238 describes a cone-and-plate device and method for determining platelet function in a primary hemostasis. In accordance with this method, a blood sample or a platelet containing fraction thereof is introduced into a
15 well-like vessel (plate member) with a flat bottom on which plasma proteins are immobilized. A cone device is then rotated in the vessel and as a result of shear forces which develop on the surface blood platelets adhere and aggregate on the plasma protein coated surface of the plate member. The platelet function can then be determined based on the pattern of adhered aggregated blood platelets.

GENERAL DESCRIPTION OF THE INVENTION

The invention has its purpose of providing an automatic apparatus and method for handling and assaying a biological specimen. The apparatus and method of the invention is useful for handling an analysis of a variety of different specimens, primarily biological specimens. One preferred embodiment of the invention concerns the assaying of blood or a platelet-containing fraction thereof, for the purpose of determining platelet function. However, the invention is not limited to this specific embodiment.

The invention provides, by a first of its aspects, an apparatus for analyzing a liquid body-specimen, the apparatus comprising: at least one specimen handling station for receiving one specimen carrying device adapted for holding the specimen; an imaging station fitted with an optical image capturing device for analyzing the specimen; an imaging station fitted with an optical image capturing device for analyzing the specimen; a carriage fitted with a specimen carrying device receptacle for engaging the specimen carrying device and for displacing it between the specimen handling station, the imaging station and an unloading station; and an incremental displacement mechanism for displacing the at least one specimen carrying device once in said imaging station or said image capturing device to permit said capturing device to selectively obtain images of two or more locations of said specimen.

The specimen carrying device may be any device that can retain a liquid specimen. A particular embodiment is a device that includes a well for retaining the specimen. In accordance with a particular, non-limiting embodiment of the invention, the specimen carrying device is of the cone-and-plate type.

In accordance with another of its aspects the invention provides a kit for use with liquid body-specimen and an analyzer, the kit comprising:

- (One) at least one cone-and-plate couple; and
- (Two) a waste container.

In accordance with one embodiment, the kit comprises liquids for introduction into the well with the specimen, for example, a preparation that

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contains an anti-coagulant agent. The kit may also comprise replacement tubings for the apparatus as well as replacement liquid and waste containers used with the apparatus. The kit will typically also include an instruction manual to be holders.

In accordance with another aspect the invention provides a specimen
5 carrying device comprising a well for holding a specimen and an engagement portion for engaging with a rotary motor of a specimen analyzing apparatus for rotation of the device by said motor.

Yet by another aspect of the invention there is provided a method for analyzing liquid body-specimens, the method comprising the following steps:

- 10 (One) obtaining a liquid body-specimen analyzer comprising at least one specimen handling station for obtaining preparation on a specimen carrying device, an imaging station fitted with an optical image capturing device, a carriage fitted with a specimen carrying device receptacle and being displaceable between a loading station, and an
15 unloading station with respective positions at said stations, and a programmable controller;
- (Two) engaging the specimen carrying device with the carriage;
- (Three) obtaining a specimen of body liquid and introducing it on the specimen carrying device;
- 20 (Four) displacing the carriage from the loading station to the at least one specimen handling station so as to obtain a preparation;
- (Five) advancing the carriage to the imaging station and displacing one of the specimen carrying device and imaging device for obtaining consecutive images of the preparation;
- 25 (Six) displacing the carriage to the unloading station for disposal of the specimen carrying device.

Said specimen handling station is designed to receive at least one specimen carrying device and is adapted for holding the specimen. The specimen carrying device, at times, *a priori*, already filled with a specimen, is loaded to the apparatus
30 at the specimen handling station.

In accordance with one embodiment, said unloading station is the same as said specimen handling station and accordingly, at the end of the procedure, the specimen carrying device is returned to this station for unloading and disposing said device into a waste receptacle typically located at said unloading station.

5 Said incremental displacement mechanism, may provide for displacement of said specimen carrying device in one of a plurality of coordinate systems, for example an X-Y coordinate system, a polar coordinate system or an angular coordinate system. Depending on the mechanism, a programmed or programmable controller may displace the carrying device according to a different protocol.

10 In accordance with a preferred embodiment of the analyzing method, at the handling station of step (d) the plate member is retained stationary and the cone member is rotated against the plate member for mixing the specimen.

Furthermore, at step (e) the plate member is rotated at regular angular intervals so as to obtain a plurality of consecutive images of the preparation, said
15 images being captured by the optical image capturing device. For that purpose, at step (e) the specimen carrying device is placed offset with respect to a longitudinal axis of the imaging device.

The apparatus typically includes also a mechanical handling station for mixing, inducing shearing force or agitating the specimen. In the case of the cone-
20 and-plate couple, at this station the cone is introduced into the well within the plate and rapidly revolved about its axis.

The apparatus typically includes one or more of a coloring station for introducing a specimen coloring agent onto the specimen; a rinsing station for rinsing the specimen carrying device; and a drying station for drying the specimen.
25 It should be noted that while it is possible to have, in accordance with one embodiment, different stations to perform these functions in different zones of the apparatus, according to other embodiments, all stations are combined into a single station at one zone of the apparatus. In other words, in accordance with the latter embodiment, different functions will be carried out sequentially at the same
30 location within the apparatus.

The specimen may be, *a priori*, introduced onto the device, or alternatively, the collected specimen is fed into the apparatus after it is placed at the specimen handling station.

According to a particular embodiment of the invention, the apparatus is
5 adapted for capturing several consecutive images of the preparation. For that purpose, once the specimen carrying device with the preparation is introduced into the imaging station, either one or both of the optical device, typically a microscope, or the specimen carrying device, namely the plate member of a cone-and-plate couple, is angularly displaced for obtaining a plurality of consecutive images of the
10 preparation. For this purpose, it is desirable that the specimen carrying device be positioned offset with respect to the longitudinal axis of the optical device.

For monitoring and controlling rotation and angular displacement of the plate member during the imaging process, it is formed with indicia for communication with corresponding sensors. These indicia may be in accordance
15 with one embodiment, a plurality of marks or, in accordance with another embodiment, a plurality of recesses according to which the sensors are optical-type sensors which detect sequences of light interference or light reflections as the plate member rotates.

The invention is further concerned with providing a cone-and-plate couple
20 (specimen carrying device) for use in conjunction with an analyzing apparatus in accordance with the present invention. In accordance with this application, the plate member is a well-like shaped member formed with a substantially flat and smooth base surface with a cylindrical wall upwardly extending therefrom. The cone member is formed with a conical forehead and a cylindrical rim portion
25 snugly receivable within the plate member. During a mixing process of the specimen, it is important to retain a fixed geometry between the forehead of the cone member and the base of the plate member. For this purpose, during a mixing process, a tip of the forehead of the cone member engages the base of the plate member. Preferably, at least the base surface of the plate member is transparent or

at least translucent. For best results, at least the base surface is made of a uniform-density material, for reducing light fraction and obtaining high quality images.

Preferably both the plate member and the cone member are formed with indicia for communication with corresponding sensors. Typically said indicia are a plurality of recesses or grooves or laterally extending wing members, formed at regular intervals for detection by corresponding optical sensors (light emitting/receiving type sensors).

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, some specific embodiments of the invention will now be described, by way of non-limiting examples only, with reference to the accompanying drawings, in which:

Fig. 1 is an overall view of the analyzing apparatus in accordance with the present invention, the apparatus being installed with liquid containers and a waste container, fitted with suitable tubing; the apparatus illustrated with its carriage member at the imaging station;

Fig. 2 is an overall view of the apparatus, from a different view, illustrating it in a standby, loading station, and a cone-and-plate couple, for use in conjunction therewith;

Fig. 3A is a partially sectional isometric view of a cone member of a cone-and-plate couple, for use in conjunction with an analyzing apparatus of the present invention;

Fig. 3B is a partially sectioned isometric view of a plate member of a cone-and-plate couple, for use in conjunction with an analyzing apparatus of the invention;

Fig. 4A is an isolation of the carriage and a plate member for use in conjunction with the analyzing device of the invention;

Fig. 4B illustrates the carriage of Fig. 4A with a plate member received thereby;

Fig. 4C is a partial top elevation of the carriage, without a plate member;

Fig. 5A is a top isometric view of a specimen handling assembly;

Fig. 5B is a bottom isometric view of the specimen handling assembly;

Fig. 6 is an exploded isometric view of the specimen handling assembly,
5 namely a mixing station, dyeing and rinsing station and drying station;

Fig. 7 is a sectional view of the cone-and-plate couple received within the
mixing station during a mixing procedure;

Fig. 8 is a sectional view of a plate member received at the dyeing and
rinsing station;

10 **Fig. 9** is a sectional view of a plate member received at the drying station;

Fig. 10A illustrates a portion of the analyzing apparatus at a first stage of
loading a cone-and-plate couple;

Fig. 10B illustrates a portion of the analyzing apparatus at a cone engaging
mixing stage;

15 **Fig. 10C** illustrates a portion of the analyzing apparatus with the carriage at
the dyeing and rinsing station during a dyeing or rinsing stage;

Fig. 10D illustrates a portion of the analyzing apparatus with the carriage at
the drying station during a drying stage;

Fig. 10E illustrates a portion of the analyzing apparatus with the carriage at
20 the imaging station;

Fig. 11A illustrates the analyzing apparatus at a first stage of unloading and
disposing of a plate member;

Fig. 11B illustrates the analyzing apparatus at a second stage of disposing
the plate member; and

25 **Fig. 11C** illustrates the unloading and disposing of a cone member.

DETAILED DESCRIPTION OF SOME SPECIFIC EMBODIMENTS

Attention is first directed to Figs. 1 and 2 of the drawings illustrating the
analyzing apparatus of the present invention at two respective views for visualizing
30 various components of the apparatus generally designated **20**. The apparatus is

assembled on a support construction comprising a base plate **22** and a rear plate **24** to which the various components of the apparatus are attached. For the sake of clarify a cover of the apparatus is removed. The apparatus comprises several main sub-assemblies, namely a specimen handling assembly generally designated **28**, an
5 imaging station **30**, a carriage **32** displacingly mounted on a horizontal leading rail and being displaceable therealong by means of motor **36** fitted with an encoder **38**.

A controller **39** fitted with a processor, a keypad, a display and a printer is provided, which is either fixed to the device or a portable device (wire or wireless communication with the device). Function of the controller will be discussed in
10 somewhat more detail hereinafter. Typically but not necessary so, the controller is programmable such that several examination routines and procedures may be programmed and stored.

The apparatus further comprises a suction pump **40**, a vacuum container **42**, a dyeing agent container **44**, a rinsing liquid container **46**, a dyeing agent pump **48**,
15 a rinsing liquid pump **50** and a waste container **52**.

For the sake of clarity, flexible tubing extending between the various components is illustrated in dashed lines and is represented only in Fig. 1. A first tube **56** extends between vacuum pump **40** and vacuum container **42**. Another tube **58** extends between the vacuum container **42** and a three-way valve member **60**, from which one tube **64** extends to a drying assembly **66** and another tube identified as **68** leads to a coloring and rinsing station **70**. Three way valve **60** may be replaced by other control valve means, as known *per se*. Dyeing agent is drawn from a container **44** by means of a tube **74** extending through peristaltic pump **48** and then extends to the coloring and rinsing station **70**. Rinsing liquid is
25 transferred to the coloring and rinsing station **70** by means of tube **78** extending through peristaltic pump **50**. A waste disposal tube **75** extends between the vacuum container **42** and waste container **52**. This tube, according to an embodiment of the invention, is a fixed, rigid tube. Tubes **74** and **78** are flexible, disposable tubes, which are periodically replaced. Other tubes are periodically
30 replaced, as may be required.

It is to be appreciated that the various components of the apparatus, e.g. pumps, sensors, motors, imaging and capturing device, are connected to the controller 39, the latter receiving all input data and issuing responsive control signals. Communication with the controller 39 may be by wire or wireless means. 5 Alternatively, the controller may be integrally mounted on the device with suitable wiring or communication means.

Prior to providing further detailed explanations concerning the analyzing apparatus of the present invention, further reference will be now directed to Figs. 3A and 3B for illustrating the structure of a cone-and-plate couple (specimen 10 carrying device) adapted for use with the apparatus 20 in accordance with the present invention. Fig. 3A illustrates the cone member generally designated 90, having a generally cylindrical shape with cylindric side walls 92 and a forehead 94 tapering at an angle of about $2\frac{1}{2}^\circ$. Laterally extending from the top of wall 92 there is a skirt portion 96 which in the present embodiment is divided into three 15 sectors, the purpose of which will become apparent hereinafter. However, it is noted that a bottom surface 98 of said skirt portion is essentially flat and smooth. As can further be seen in Fig. 3A, the cone member comprises a coaxially extending stem 100 having a tapering cross-section for engagement with a chuck at the mixing station 28 as will become apparent hereinafter.

20 A plate member generally designated 110, illustrated in Fig. 3B, has a well-like portion 112 with an essentially smooth and flat base surface 114, from which upwardly extends a cylindrical wall 116 having an upright inner-wall 117, terminating at smooth and flat edge 118. A laterally extending geared rim 122 is concealed by a lateral skirt 124, said geared rim 122 adapted for engagement with a 25 rotation mechanism fitted on the carriage 32 as will become apparent hereinafter. In accordance with an embodiment of the invention, at least the base surface 114 of the plate member 110, is transparent or at least translucent. Base surface 114 is essentially parallel to the lateral skirt 124, such that when the plate member is received at the imaging station, the base surface extends normal to a longitudinal

axis of the imaging device i.e., to the line of sight thereof, so that images obtained are in focus, also after the plate member **110** is rotated.

Formed at a lower end of the plate member **110** there is a crown-like recessed portion **128** adapted for cooperation with an optical sensor fitted at the carriage **32**, as will become apparent hereinafter.

Whilst the particular apparatus described in the present embodiments and the specimen carrying device disclosed in the specification refer in particular to a cone-and-plate couple, it is to be appreciated that other types of specimen carrying devices may be used with the necessary arrangements being made at the analyzing apparatus, *mutatis mutandis*.

With further reference to the Figs. 4A-4C, it is noticeable that the carriage **32** is fitted with a flat motor unit **140** (a flat motor in the present example) rotating an output pinion **142** engaged with a transmission gear **144**.

Carriage **32** comprises a specimen carrying device receptacle **150** which in the present embodiment is a U-shaped aperture formed in the carriage **32**, with the arms of the U-like shape extending to an end **152** of the carriage. The carriage is also fitted with a pair of springy retention arms **156** for gripping annular skirt **124** of plate member **110**, as illustrated in Fig. 4B.

As can be seen best in Fig. 4C, the transmission gear **144** extends into the receptacle **150** at the circular portion thereof, at a location which is offset from center line **160**. The location of the transmission gear **144** and its rotation in the direction of arrow **162** ensure that the plate member **110** is biased to an inward position as in Fig. 4B, to a fixed location within the receptacle **150**.

As further seen in Fig. 4A, the carriage **32** is fitted at a bottom face thereof with an optical sensor **170** which when the plate member **110** is received in the receptacle **150**, as in Fig. 4B, the sensor is capable of detecting and monitoring angular displacement of the plate member **110**. The sensor **170** is of the type provided with a light source and a light sensitive device which detects the recesses formed in the crown-like bottom portion **128** (Fig. 3B) of the plate member **110** and

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by means of the controller 39 connected to the sensor, the precise angular displacement of the plate member 110 over the carriage 32 may be derived.

Referring now back to Figs. 1 and 2, the carriage 32 is displaceable about the horizontal rod 34 by means of motor 36 and encoder 38 for precise displacement of the carriage 32 and location thereof at each of the respective stations, and it is thus apparent that encoder 38 is connected to the controller 39.

For better understanding of the sub-assemblies of the specimen handling assembly 28, further attention is directed to Figs. 5A, 5B and 6, in which the three preparation stages are seen and comprising a mixing station 29, a dyeing and rinsing station 70 and a drying station 66, all mounted on a carrying platform 180 supported by an arm 182. Arm 182 is fixedly attached by bolts (not shown) to a bracket 183 which in turn is slidable about a vertical profiled rail 184, which is secured to rear plate 24 of the device. Bracket 183 is slidingly articulated to rail 184 in a precise manner as known *per se* and is vertically displaceable thereabout by means of motor unit 190. Motor unit 190 is also connected to the controller and is fitted with an encoder 191. Alternatively, or in combination with the encoder, there may be provided one or more limit sensors (not shown).

As can best be seen in Fig. 6, the mixing station 29 comprises a motor 186 fitted with a central hollow shaft 188 through which extends an indicator pin 189 which is freely displaceable within the hollow shaft 188 between a retracted position in which it does not project from a top surface of block 194 and an extracted position in which its upper edge projects from the top surface of block 194 and is then detectable by optical sensor 196.

With further reference also to Fig. 7, it can be seen that motor 186 is supported over a support ring 200 and the entire structure is fixed by studs 202. Received within ring 200 there is an extension sleeve 203 rotatably engaged to rotary hollow shaft 188 of motor 186. A chuck (referred to also as a collet) 206 is rotatably fixed within sleeve 203, said chuck formed at lower end thereof 208 with a tapering section adapted for friction engagement with the corresponding tapering

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stem member **100** of cone member **90** (Fig. 3A). Chuck **206** is received within a pressure ring **210** which is axially biased in a downward direction by means of coil spring **212** having an upper end thereof bearing against a rim **214** of sleeve **203** and at a lower end thereof bearing against an annular groove formed at ring **210**. The arrangement is such that the chuck **206** is rotationally engaged with motor **186** but, on the other hand, the chuck has some axial freedom.

This arrangement provides some biasing force applied to the cone member **90** when it is engaged within chuck **206**, which force gives rise to a light pressure of the cone member **90** over the plate member **110**, required for proper laminate low formation procedure by the cone-and-plate device, as known *per se*.

Fitted below carrying platform **180** there is an optical sensor **220** which extends at a position such as to detect and monitor location and rotation of a cone member **90**. Optical sensor **220** is fitted with an integral light source and a light detector and is capable of sensing light intermissions caused by reflection of the segmented skirt portion **96** of the cone member **90**.

Articulated to rear plate **24** is an ejector arm **225** which serves to eject the cone member **90** in a manner to become apparent hereinafter.

Dyeing and rinsing station **70** (see also Fig. 8) comprises a suction pipe **230** connectable by a flexible tube **68** (see Fig. 1) to refuse vacuum container **42**. Pipe **230** is rigid and at the operative suction position (see Fig. 8) it extends essentially to the bottom surface **114** of plate member **110** leaving only a clearance therefrom.

Coloring and rinsing assembly **70** further comprises a pipe holder **234** fitted for receiving flexible tube **78** extending from rinsing liquid container **46** and a second tube **74** extending from dyeing agent container **44**. The arrangement is such that an end **238** of tube **78** is received within plate member **110** and it is directed so as to generate an essentially tangent flow of rinsing liquid. It is to be noted that pipe holder **234** together with the flexible tubes **74** and **78** are all disposable and typically constitute components of a diagnostic kit, as will be discussed hereinafter.

Fitted at a bottom surface of carrying platform **180** there is a liquid level sensor carrier plate **242** from which extend three coiled spring-like electrodes **224**, **226** and **228**, the first two of which extend downwards to a level which corresponds practically with the bottom surface **114** of plate member **110** though leaving a clearance therefrom, and the third electrode **228** extending adjacent an upper edge of the cylindrical wall portion **116** of plate member **110**. The arrangement is such that electrode **224** serves as a neutral electrode whilst electrode **226** serves as a minimum liquid level sensor and electrode **228** serves as a maximum liquid level sensor by closing therebetween an electric circuit, as known *per se*.

Further attention is now directed to the drying station **66** with further reference being made also to Fig. 9. The drying assembly comprises a plug member **250** fixedly attached to carrying platform **180** by bushings and bolts collectively designated **253**. The plug **250** is connected via tube **64** (see Fig. 1) to three-way valve **60** from which tube **58** extends to the vacuum container **42**. Plug **250** is formed with a throughgoing bore **252** extending to its forehead **254** which is essentially flat. In the present embodiment bore **252** is coaxial within the cylindrical plug **250**. Formed at its lower end there is a rim **258** fitted for snugly receiving within the well portion **112** of the plate member **110** (Fig. 9), however, leaving a narrow interstice between the rim **258** and the inner wall surface **117** of plate member **110**.

Plug **250** is further formed with a laterally extending shoulder portion **262** having a bottom surface **264** so that in the operative position as in Fig. 9, surface **264** comes to rest over upper rim **118** of the plate member **110**, thus leaving a minimal clearance between forehead **254** and surface **114** of plate member **110**, the purpose of which will become apparent hereinafter.

Furthermore, the lateral shoulder **262** is formed with at least one air inlet port **268** extending into a peripheral annular groove **270** such that when a vacuum is generated via bore **252** it gives rise to suction forces essentially all over the clearance between the forehead **254** and the surface **114**, for optimal drying of the

plate member **110**, such that even low flow rate suction entails smearing of the droplets of liquid which together with rotation displacement of the well during a drying process, increases drying speed and efficiency.

Further attention will now be directed to Figs. 10A to 10E for understanding
5 how a diagnostic procedure in accordance with the present invention is carried out using a diagnostic apparatus **20** in accordance with the present invention, in conjunction with a cone-and-plate couple **90** and **110**, respectively.

At a first step, the system is set to an initial stage by use of the controller **39** (Fig. 1). Upon initiation of a diagnostic procedure, the system performs several
10 self-tests, e.g. to determine sufficient dyeing agent in container **44**, rinsing liquid in container **46**, presence of a waste container **52** and to confirm that all other assemblies of the apparatus are in order. The system will also perform a test to confirm that the service door (not shown) of a cover of the device (also not shown) is closed. Upon termination of the self-tests, the carriage **32** displaces into its
15 standby position and upon request, e.g. striking a key of the controller, the carriage displaces to the loading station, by means of motor **36**, wherein receptacle **150** is accessible through the service door (not shown).

A cone-and-plate couple **290** in the assembled position is located within the receptacle **150**, as illustrated in Fig. 10A, where springy retention arms **156** bias on
20 rim **124** of the plate member **110**. Using one's finger, the cone-and-plate assembly **290** is pushed in as far as possible. Then, the service door is closed and the carriage **32** displaces to a position in which it extends below the mixing station **29**. The controller generates a control signal to rotate transmission gear **144** in direction of arrow **162**, thus confirming a true position of the cone-and-plate
25 assembly **290** and testing the sensor **170** (Fig. 4A) to recognize angular displacement of the plate member **110** as explained hereinabove.

At the next step (Fig. 10B), carrying platform **180** is displaced downwards by means of electric motor **190**, entailing sliding displacement of bracket **183** about profiled rail **184**, to a position in which chuck **206** of mixing sub-assembly **29**
30 engages with the stem **100** of cone member **90**, as in the position of Fig. 7.

Engagement of chuck **206** with the cone member **90** takes place upon axial displacement against the biasing effect of coil spring **212**. Upon said engagement, the platform **180** rises to its upper position as in Fig. 10A. Optical sensor **196** extends opposite an opening **195** formed in the block **194** and the arrangement is
5 such that when cone member **90** is engaged within the mixing sub-assembly **29**, indicator pin **189** is engaged from below by the stem portion **100** of the cone member **90**, resulting in that an upper end of indicator pin **189** projects through opening **195** and is then detected by sensor **196** which in turn generates a corresponding signal to the controller **39**, confirming correct position of the cone
10 member **90**. If, however, the cone member is not properly engaged or in case it accidentally disengages from the chuck **206**, a suitable alert signal will be generated.

Upon successful engagement of the cone member **90**, the carriage **32** returns to the loading station (as in Fig. 10A) and a suitable note appears on a display panel
15 of controller **39** (with or without a signal tone) calling for the operator to enter an identification code of the specimen and then to introduce a specimen into the well portion **112** of plate member **110**. This is followed by entering a suitable command to the controller, upon which carriage **32** returns to its position below mixing sub-assembly **29**, as in Fig. 10B.

20 Carrying platform **180** is then lowered by means of motor **190** to a position in which the cone member **90** is received within plate member **110**, at a position at which the tip of the forehead of the cone member engages the base of the plate member, as illustrated in Fig. 7. Then, motor **186** is activated so as to spin the cone member **90**, giving rise to mixing of the specimen. During rotation of cone
25 member **90**, sensor **220** detects and confirms rotation of the cone member **90** at a predetermined speed, so as to ensure proper engagement between the cone member and the chuck assembly of the motor. The cone member is rotated at a pre-selected speed which depends on the examined specimen and geometry of the cone-and-plate couple, for obtaining a laminar flow-profile and best shear results of the liquid
30 specimen (e.g. blood) about the entire cross-section of the plate member **110**, thus

obtaining an essentially homogenous smear of the liquid on the surface **114** of the plate member **110**.

The cone member is rotated at the above speed for a predetermined period of time, determined by the examined specimen, and then the carrying platform **180** is raised, thus separating between the cone member **90** and the plate member **110**. By means of sensor **196**, as explained hereinabove, the controller verifies that the cone member **90** remains engaged with the mixing sub-assembly **29** and has not adhered by means of sheer force, to the plate member **110**.

It was found that for blood platelet analysis the mixing stage should last about 2 minutes at a speed of about 720 RPM. For various specimens such as blood, other body cells or bacteria the mixing stage may last about 10 to 60 minutes, and the speed may vary between as slow as about 50 RPM to as fast as about 30,000 RPM.

At this state, the specimen is essentially homogeneously smeared on the surface **114** of the plate member **110**. The carriage **32** then displaces to the position seen in Fig. 10E, in which the plate member **110** reaches the imaging station **30**, comprising a microscope **300** and an image capturing device **302**, typically a digital camera. At this situation the LED light source **301** is activated and the system scans the surface **114** of plate member **110**, to determine by measuring light parameters transmitted through the transparent or translucent base surface **114** of the plate member. This step confirms that the specimen has indeed been introduced into the plate member **90**. In case there is a specimen in the plate member, the amount of light transmitted therethrough will obviously be less and thus different light parameters will be obtained, indicating the presence of a specimen.

From the imaging station **30**, carriage **32** returns to the dyeing and rinsing sub-assembly **70** (Fig. 10C). Carrying platform **180** then descends to a dyeing and rinsing operative level as in Fig. 8. Then, peristaltic pump **50** is activated with a rinsing liquid flushing well **112** of plate member **110**, whereby simultaneously vacuum pump (Fig. 1) is activated, giving rise to vacuum built up within vacuum container **42**. It is pointed out that at this stage the three way valve **60** is set such

that it is directed to the drying sub-assembly 66, i.e. at this stage there is no suction from the dyeing and rinsing station 70.

By means of electrodes 224, 226 and 228 (Figs. 5B, 6 and 8), the controller determines the level of rinsing liquid within the well 112 of plate member 110, until
5 the well 112 is filled at a predetermined level. Then, after a short delay, the three way valve 60 is opened so as to give rise to suction of the liquid from the plate member 110 through pipe 230 and then via tube 68 into vacuum container 42.

This rinsing procedure takes place several times (e.g. 6-8 times), and then a similar procedure takes place, though this time instead of introducing rinsing liquid,
10 a dyeing agent is propelled from container 44 via tube 74 into the well 112 of plate member 110, by means of peristaltic pump 48. This procedure takes place several times, typically twice and after the last dyeing procedure, the dyeing agent remains in the plate member 110 and the carrying platform 180 ascends, allowing the carriage 32 to displace to the drying station 66 as in Figure 10D.

15 As the carriage 32 reaches the drying station 66, the three way valve 60 is shifted into a so-called drying state in which vacuum through tube 58 and then tube 64 is applied to the plug 250, whilst the motor 140 rotates the plate member 110. Rotation of plate member 110 is confirmed by means of optical sensor 170 (Fig. 4A) as discussed hereinabove. The drying procedure takes place by applying
20 a low flow rate suction through the plug 250, which owing to the tight clearance between the opposing surfaces of the plug and the surfaces of the well portion 112 of plate member 110, cause smearing of the liquid droplets and drying of the surface 114.

After a predetermined period of time in which the plate member 110 is
25 assumed to be dry, the motor 140 and the vacuum pump 40 are stopped and then carrying platform 180 raises so as to disengage the drying assembly from the plate member. The carriage 32 is displaced to the imaging station 30 as in Fig. 10E and the three-way valve 61 is then opened to admit free liquid flow from vacuum container 42 to waste container 52.

In the present embodiment, the imaging device is a microscope **300**, with LED illumination source **301** below the carriage and it is fixed to the rear plate **24** by means of mounting bracket **310**. However, the arrangement is such that as the carriage **32** reaches the imaging station, as in Fig. 10E, the object of the microscope **300** extends offset with respect to an axis of the plate member **110**. Preferably, but not necessarily, the object of the microscope axially extends at about midway of the radii of the base surface **114** of plate member **110**.

The controller then generates several consecutive signals giving rise to intermitted angular displacement of plate member **110** by means of motor **140**. Each time the motor stops, a corresponding signal is issued to image capturing device **302** to capture an image via the microscope **300**. In this manner, statistical image sampling of the preparation is obtained, as much as may be required.

However, it should be obvious to a person versed in the art that rather than angular displacement, the plate member or the imaging device may be displaced about an X-Y coordinate system, or about a polar coordinate system, whereby several consecutive images are obtained for reaching statistical analyses of the preparation.

Upon completion of the image sampling process, carriage **32** displaces to an unloading station (Fig. 11A) wherein carrying platform **180** is lowered to a position in which the cone member **90** is at least partially engaged within plate member **110** and then the carriage **32** displaces in a direction of arrow **304**, towards the dyeing and rinsing assembly **70** (Fig. 11B) giving rise to disengagement of the plate member from the receptacle **150** of carriage **32**, allowing it to fall into waste container **52** via its aperture **306**.

Then, the carrying platform **180** is elevated by means of motor **190** until a position in which an upper end of indicator pin **189** engages the ejector arm **225** resulting in axially displacing of the cone member **90**, disengaging it from the chuck assembly and allowing it to fall into waste container **52** via opening **306**.

At this state, the controller sets the system to a standby position allowing data to be processed by a suitable processor to display and print the analysis results.

The controller will simultaneously perform tests to determine sufficient liquid level in the liquid containers, determining that the waste container **52** is not full, etc.

A dyeing agent may sometimes dry and clog the tubes. Accordingly, it is advantageous to replace periodically some of the components.

5 It is in accordance with a further aspect to provide a kit for use with a diagnostic device in accordance with the present invention. Such a kit will typically comprise one or more cone-and-plate couples together with replacement flexible tubes, waste container **52** and fresh liquid containers (dyeing agent container **44** and rinsing liquid container **46**). Where a printer is provided for
10 printing the analysis results, the kit may include also an ink cartridge for the printer, as well as a supply of paper.

The controller may have several pre-programmed or programmable functions, setting as an example a timer which if detecting a lapse between one analysis and a consecutive analysis, say more than 15 minutes, the peristaltic
15 pumps **48** and **50** operate in a reverse direction so as to propel the dyeing agent and rinsing liquid into their respective containers **44** and **46**, to prevent clogging of the piping. In such a case, upon reactivation of the system, suitable measures have to be taken to propel sufficient liquid into the system upon deactivation thereof.

In order to prevent usage of non-genuine disposable components, in particular a cone-and-plate couple, the plate member **110** may be provided with
20 some sort of encoding which may be detectable by the imaging system. Such encoding may either be a complicated printed pattern or other sort of encryption which only upon identification by the imaging system and certification by the controller, the device will perform an analysis. Such an encryption may be, for
25 example, imparting a pattern on the base surface **114** on plate member **110**, which pattern will have to be recognized by the optical system.

CLAIMS:

1. An apparatus for analyzing a liquid body-specimens, the apparatus comprising:
 - at least one specimen handling station for receiving one specimen carrying
 - 5 device adapted for holding the specimen;
 - an imaging station fitted with an optical image capturing device for analyzing the specimen;
 - a carriage fitted with a specimen carrying device receptacle for engaging the specimen carrying device and for displacing it between the specimen handling
 - 10 station, the imaging station and an unloading station; and
 - an incremental displacement mechanism for displacing the at least one specimen carrying device once in said imaging station or said image capturing device to permit said capturing device to selectively obtain images of two or more locations of said specimen.
- 15 2. An apparatus according to Claim 1, wherein the specimen carrying device includes a well for retaining the specimen.
3. An apparatus according to Claim 1 or 2, wherein the unloading station is at the same location as said handling station.
4. An apparatus according to any one of Claims 1 to 3, wherein the
- 20 incremental displacement is about an X-Y coordinate system, a polar coordinate system or an angular coordinate system.
5. An apparatus according to any one of Claims 1 to 4, comprising one or more of: a mechanical handling station for mixing, inducing shearing forces or agitating the specimen; a coloring station for introducing a specimen coloring agent
- 25 onto the specimen; a rinsing station for rinsing the specimen carrying device; and a drying station for drying the specimen; these stations and the specimen handling station being in the same or in a different zone of the apparatus.

6. An apparatus according to any one of Claims 1-5, wherein the specimen is fed onto the specimen carrying device after same is in the specimen handling station.
7. An apparatus according to any one of Claims 1-7, wherein the at least one specimen handling station comprises at least one container holding a preparation liquid and a mechanism for feeding the preparation liquid onto said specimen carrying device, a waste container for collecting refuse liquids and used specimen carrying devices, and comprises a fluid pumping arrangements for propelling fluids.
8. An apparatus according to Claim 2, wherein the specimen carrying device is a well-like member of a cone-and-plate couple and wherein at the mixing station the cone member is rotatable within the plate member.
9. An apparatus according to Claim 4, wherein the specimen carrying device is displaceable within the carriage member at angular increments.
10. An apparatus according to Claim 8, wherein the mixing station comprises a rotary motor that can engage a cone member of said couple and that is axially displaceable for respective introducing and removing the cone member from the plate member.
11. An apparatus according to any one of Claims 1 to 10, comprising an air pressure/vacuum source for suction of refuse liquids from the specimen carrying device and for drying at the drying station.
12. An apparatus according to any one of Claims 1 to 11, wherein the optical image capturing device comprises a microscope and a camera for capturing images of the preparation, with an objective of the microscope extending offset with respect to the specimen carrying device.
13. An apparatus according to Claim 10, wherein the imaging station is fitted with a LED-type illumination source to illuminate the specimen.
14. An apparatus according to Claim 5, wherein the specimen carrying device comprises a well and the drying station comprises a cylindrical plug insatiably into the well with a forehead of the plug being essentially flat and having a diameter

snugly receivable within the well; at least one air suction port formed at the forehead and a suitable venting inlet to admit air flow towards the forehead; the plug further comprising an axial restricting arrangement for obtaining a fixed clearance between the forehead and a base of the well.

5 **15.** An apparatus according to Claim 14, wherein the plug is formed with a peripheral air channel extending above the forehead, and being in flow communication with the venting inlet.

16. An apparatus according to Claim 14 or 15, wherein the axial restricting arrangement comprises a shoulder of the plug engageable with a corresponding seat
10 portion formed at a peripheral wall of the well.

17. An apparatus according to Claim 9, wherein the specimen carrying device is fitted with indicia for communicating with corresponding sensing arrangement, for detecting and monitoring rotary motion thereof.

18. An analyzing device according to Claim 8, wherein the well and cone members
15 are each fitted with indicia for communicating with corresponding sensors, for detecting and monitoring rotary motion thereof.

19. An apparatus according to Claim 5, wherein the coloring and rinsing station comprises a liquid introducing and withdrawal tubing and a liquid-level sensing mechanism.

20 **20.** An apparatus according to Claim 19, wherein the liquid introducing tubing is formed so as to direct liquid flow at an essentially tangent direction within the well.

21. An apparatus according to Claim 19, wherein the liquid-level sensing mechanism comprises three spring-like electrodes, two of which extend proximal the base of the well, and one at a maximum liquid level.

25 **22.** An apparatus according to Claim 7, further comprising control valving for selectively directing fluid flow between the various stations.

23. An apparatus according to Claim 7, wherein the fluid pumping arrangements comprises an air pressure/vacuum generator and one or more peristaltic pumps for propelling liquids.

24. An apparatus according to Claim 8, wherein optical sensors are provided for detecting and monitoring rotation of the well with respect the carriage and of the cone member with respect the housing of the mixing station.
25. An apparatus according to Claim 8, wherein the mixing station comprises a
5 chuck for releasably engagement with a stem coaxially extending from the cone member.
26. An apparatus according to Claim 25, wherein the stem of the cone member has a tapering cross-section corresponding with a conical cross-section of the chuck.
27. An apparatus according to Claim 2 or 8, wherein the well is formed with a
10 substantially flat and smooth base surface with a cylindrical wall upwardly extending therefrom, with an engagement portion for engaging with a rotary motor of the carriage.
28. An apparatus according to Claim 27, wherein a bottom portion of the well is formed with a geared path for engagement with a corresponding geared
15 transmission of a rotary motor fitted on the carriage.
29. An apparatus according to Claim 27, wherein the well further comprises a skirt formed with one or more recesses for association with an optical sensor detecting and monitoring rotation of the well.
30. An apparatus according to Claim 28, wherein the geared path is concealed by a
20 skirt portion laterally extending beyond the geared path.
31. An apparatus according to Claim 30, wherein the skirt portion is essentially parallel to the base surface of the plate member.
32. An apparatus according to any one of Claims 1 to 31, comprising a security arrangement for identifying the specimen carrying device and certifying its
25 matching with the analyzing device.
33. An apparatus according to Claim 32 wherein the specimen carrying device is fitted with an encryption code detectable by the imaging device.
34. An apparatus according to Claim 32, wherein the carriage is fitted with a well receptacle and a motor for imparting the well rotary motion, and arresting members
30 for engaging the well at its operative position within the receptacle.

35. An apparatus according to any one of Claims 1 to 34, wherein the receptacle of the carriage has a U-like shape, wherein the arm extensions constitute a feeding opening for the well and at an operative position the well is positioned snugly at the circular portion of the receptacle; the carriage comprises a driving gear for engagement with a corresponding geared path of the well, said driving gear extending offset with respect a longitudinal axis of the receptacle.

36. A cone-and-plate couple provided as a unit.

37. A cone-and-plate couple according to Claim 36, for use in a specimen analyzing apparatus that includes a module for initially dissociating the cone from the plate to permit introduction of a specimen into the plate and subsequently re-associating the cone with the plate.

38. A cone-and-plate couple according to Claim 36 or 37, for use in an apparatus according to any one of Claims 1 to 35.

39. A cone-and-plate couple according to any one of Claims 36 to 38, wherein the well has a substantially flat and smooth base surface with a cylindrical wall upwardly extending therefrom, with an engagement portion for engaging with a rotary motor of the carriage.

40. A cone-and-plate couple according to Claim 39, wherein a bottom portion of the plate is formed with a geared path for engagement with a corresponding geared transmission of a rotary motor fitted on the carriage.

41. A cone-and-plate couple according to Claim 39, wherein the plate member further comprises a skirt formed with one or more recesses for association with an optical sensor detecting and monitoring rotation of the well.

42. A cone-and-plate couple according to Claim 39, wherein the geared path is concealed by a skirt portion laterally extending beyond the geared path.

43. A cone-and-plate couple according to Claim 42, having a base surface that is essentially parallel to the skirt portion.

44. A cone-and-plate couple according to any one of Claims 37 to 43, fitted with a security code readable by the apparatus for identifying the plate member and certifying its matching with the apparatus.

45. A cone-and-plate couple according to any one of Claims 36 to 44, wherein the plate member is fitted with an encryption code identifying the specimen.
46. A cone-and-plate couple according to any one of Claims 36 to 45, wherein the cone member is formed with a stem portion for releasable engagement with a
5 chuck of a mixing station of the analyzing device.
47. A cone-and-plate couple according to Claim 46, wherein the stem portion of the cone member has a tapering cross-section corresponding with a conical cross-section of the chuck.
48. A cone-and-plate couple according to any one of Claims 36 to 47, wherein the
10 cone member has a conical forehead with a cylindrical wall extending therefrom, said wall snugly receivable within the plate member.
49. A cone-and-plate couple according to any one of Claims 36 to 48, wherein the cone member is restrictedly insatiable into the plate member so as to ensure a tip of the forehead of the cone member engages the base of the plate.
- 15 50. A cone-and-plate couple according to any one of Claims 36 to 50, having at least a base surface of the well that is transparent or translucent.
51. A method for analyzing liquid body-specimens, the method comprising the following steps:
- (One) obtaining a liquid body-specimen analyzer comprising at least one
20 specimen handling station for obtaining preparation on a specimen carrying device, an imaging station fitted with an optical image capturing device, a carriage fitted with a specimen carrying device receptacle and being displaceable between a loading station, and an unloading station with respective positions at said stations, and a
25 programmable controller;
- (Two) engaging the specimen carrying device with the carriage;
- (Three) obtaining a specimen of body liquid and introducing it on the specimen carrying device;
- (Four) displacing the carriage from the loading station to the at least one
30 specimen handling station so as to obtain a preparation;

(Five) advancing the carriage to the imaging station and displacing one of the specimen carrying device and imaging device for obtaining consecutive images of the preparation;

(Six) displacing the carriage to the unloading station for disposal of the specimen carrying device.

52. An analyzing method according to Claim 48, wherein during or after step (d) refuse agents used at the at least one preparation station are disposed to a waste container.

53. An analyzing method according to Claim 48, wherein the specimen carrying device is a plate and cone couple.

54. An analyzing method according to Claim 48, wherein at the handling station of step (d) the plate member is retained stationary and the cone member is rotated against the plate member for mixing the specimen.

55. An analyzing method according to Claim 51, wherein after mixing the specimen is colored and then dried.

56. An analyzing method according to Claim 50, wherein at step (e) the plate is rotated at increments so as to obtain a plurality of images of the preparation, said images being captured by the optical image-capturing device.

57. An analyzing method according to Claim 48, wherein at step (e) the plate member is incrementally angularly displaced.

58. A kit for use with liquid body-specimen analyzer, the kit comprising:

(One) at least one cone-and-plate couple;

(Two) a waste container.

59. A kit according to Claim 58, further comprising fluid transfer replacement tubing.

60. A kit according to Claim 59, further comprising a tubing holder.

61. A kit according to any one of Claims 58 to 60, wherein at least the cone member of the cone-and-plate couple is fitted with optical detectable indicia for detecting and monitoring rotation thereof.

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62. A kit according to any one of Claims 58 to 61, wherein at least one of the cone-and-plate couple is fitted with security arrangements for identification and certifying matching with the analyzing device.

63. A kit according to Claim 62, wherein the plate member is fitted with an
5 encryption indication recognizable by the analyzer.

64. A specimen carrying device comprising a well for holding a specimen and an engagement portion for engaging with a rotary motor of a specimen analyzing apparatus for rotation of the device by said motor.

65. A specimen carrying device according to Claim 64, wherein a bottom portion
10 thereof is formed with a geared path for engagement with a corresponding geared transmission of the rotary motor.

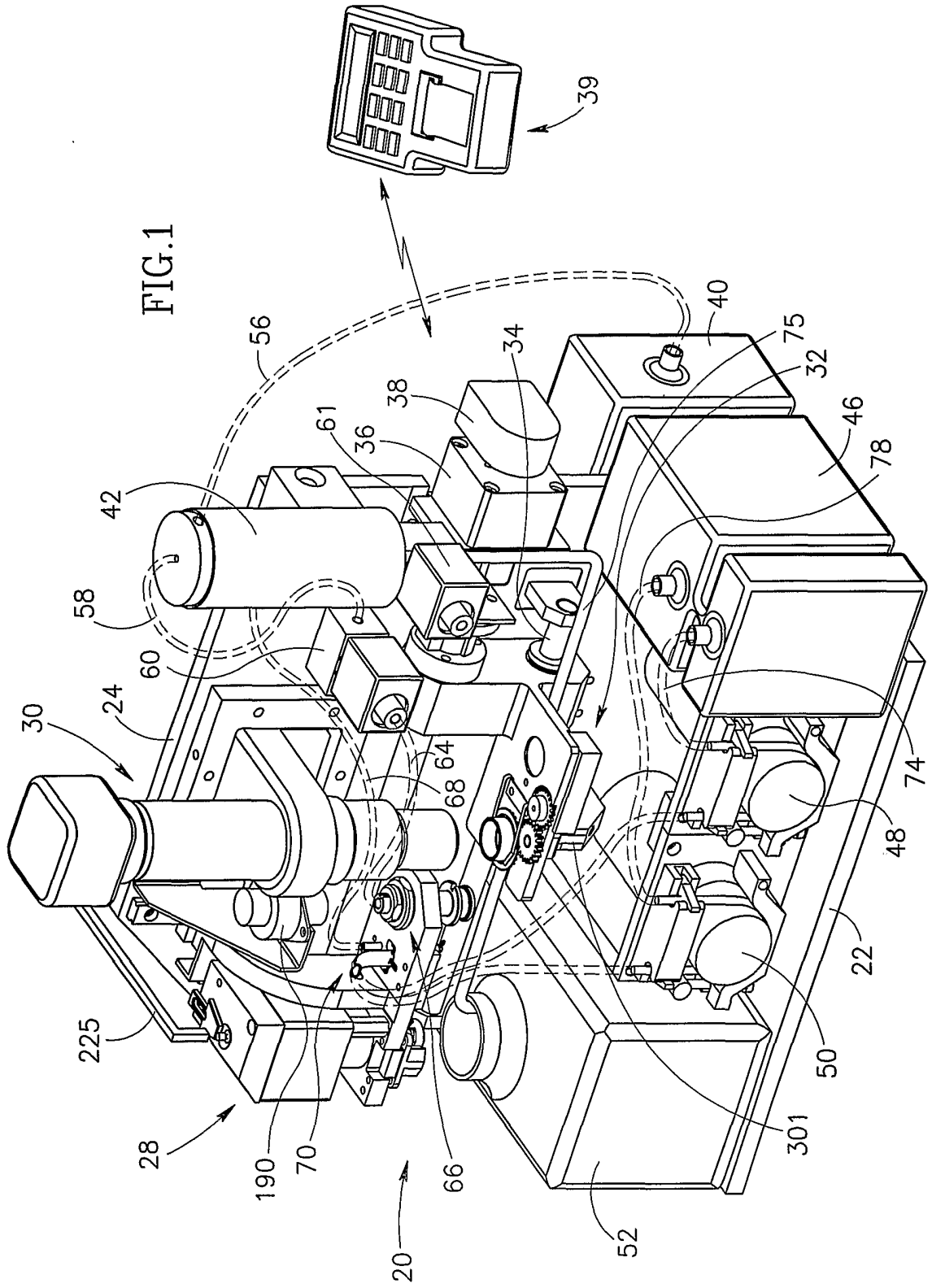
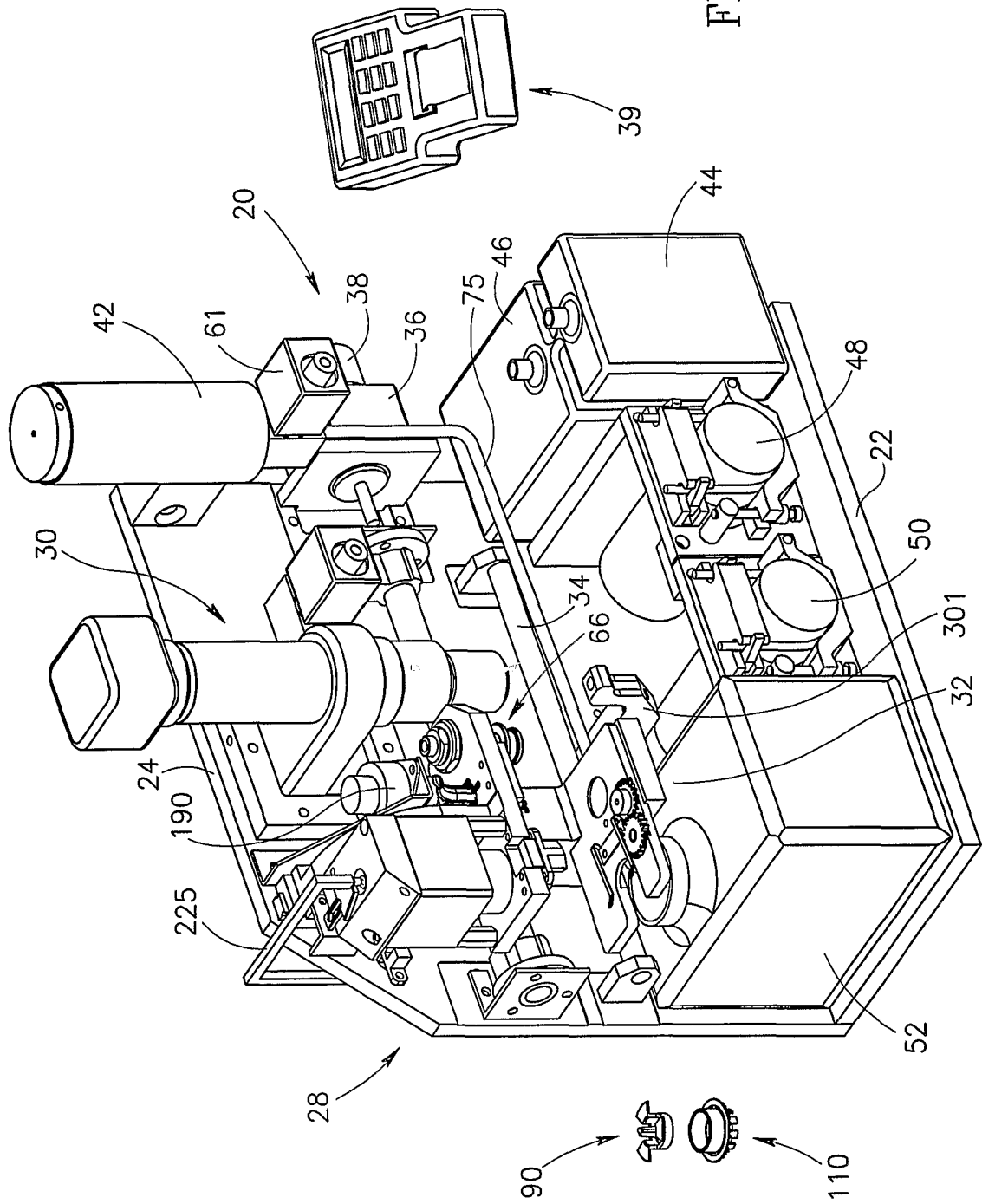


FIG. 2



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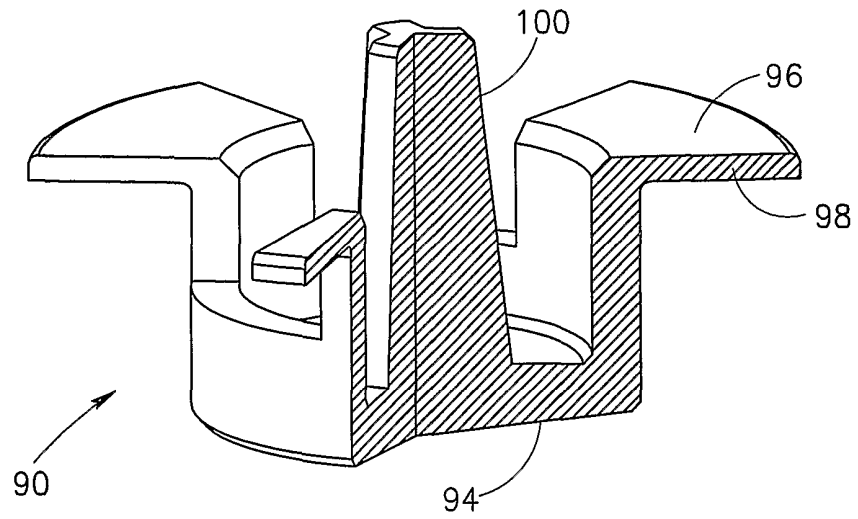


FIG. 3A

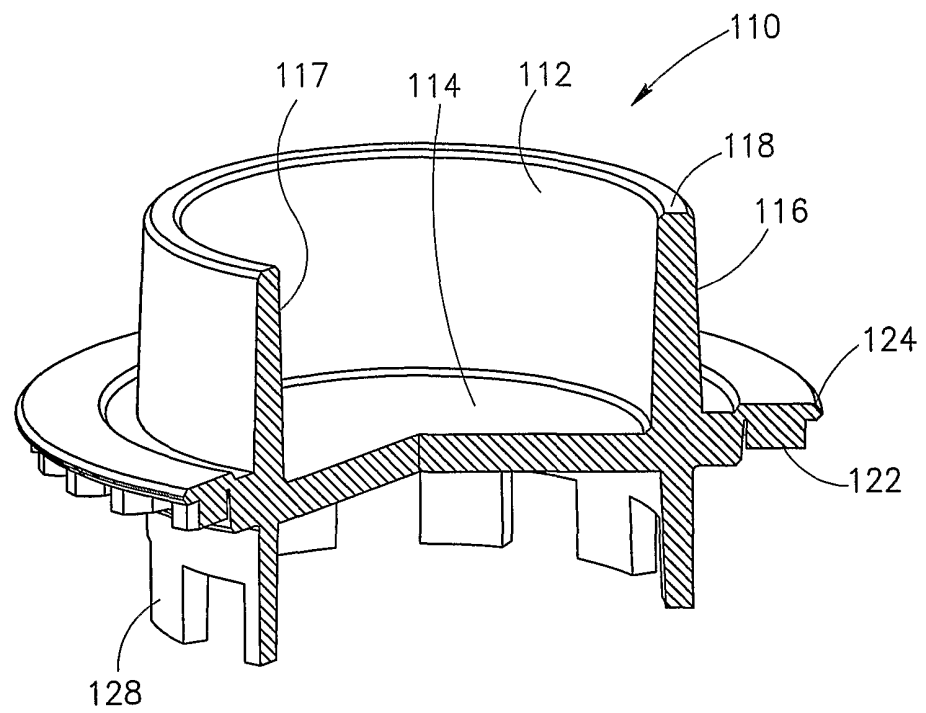


FIG. 3B

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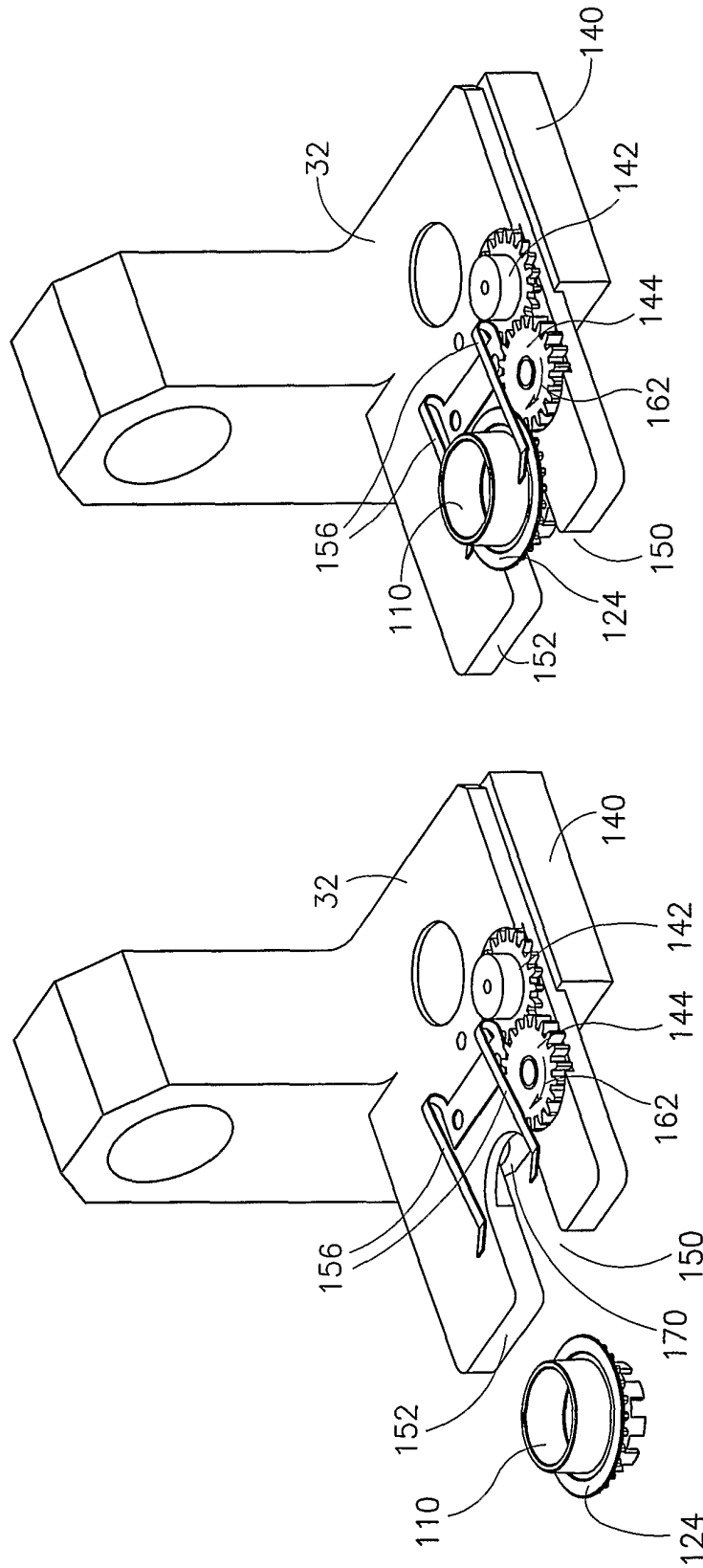


FIG. 4B

FIG. 4A

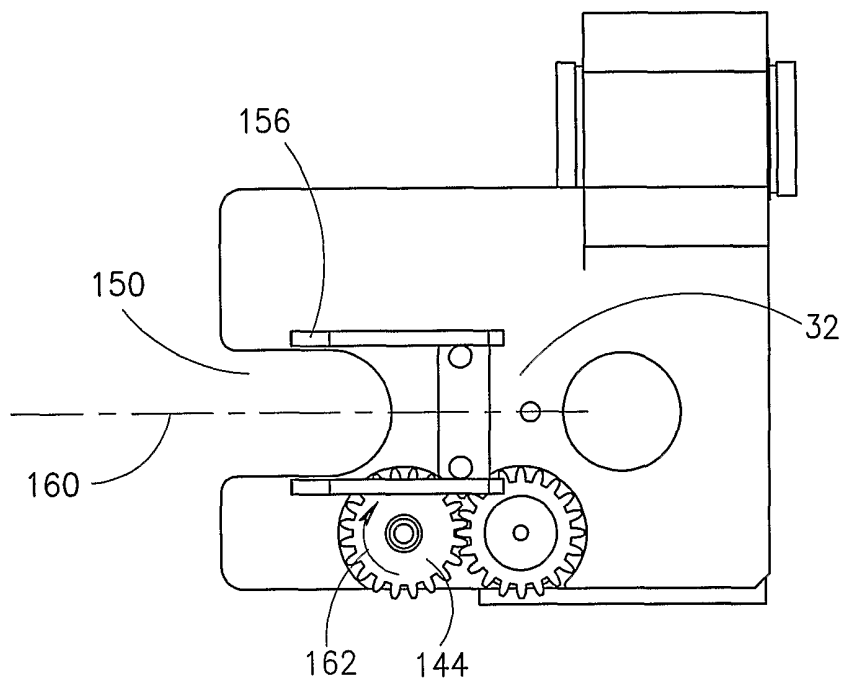


FIG.4C

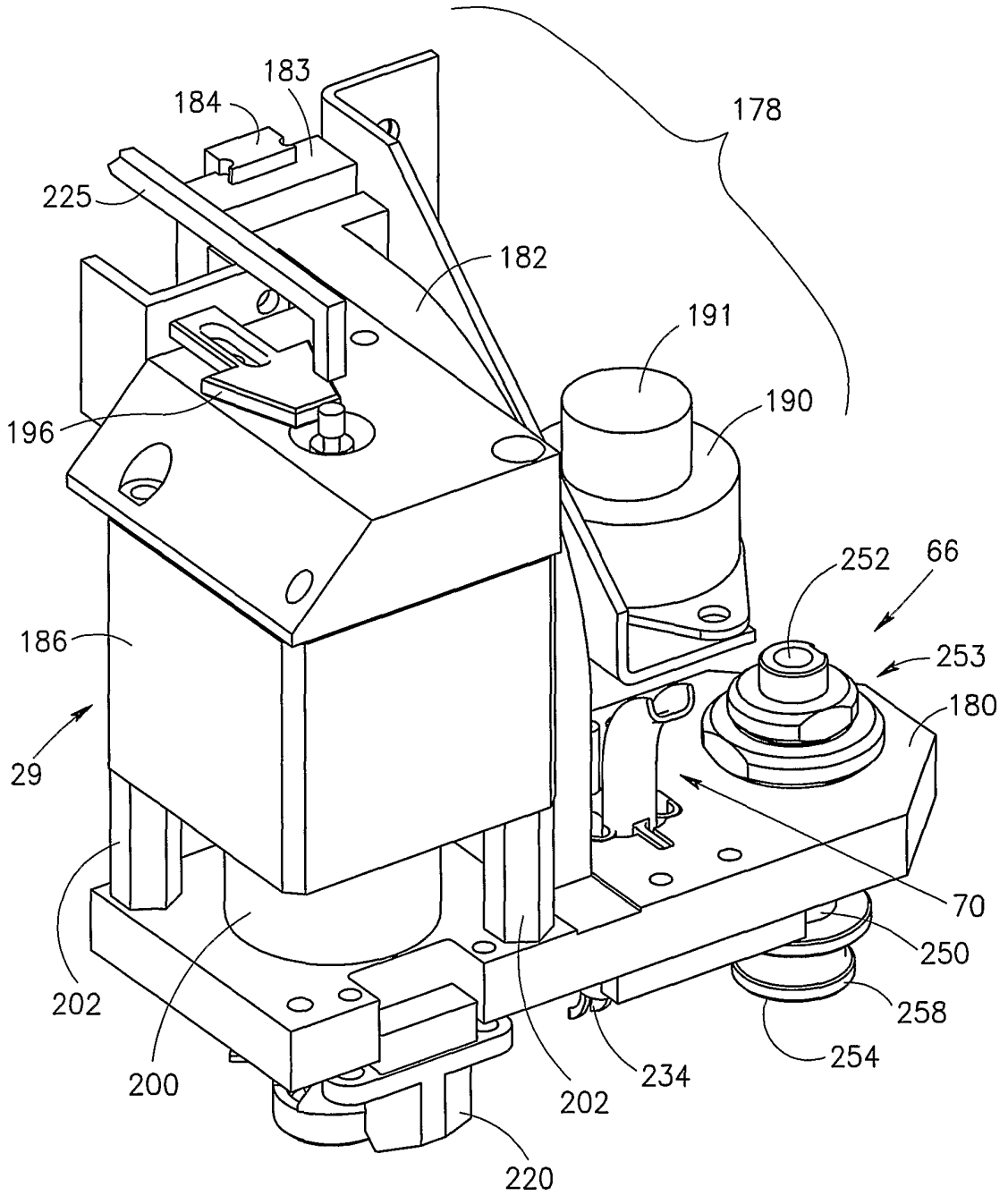


FIG. 5A

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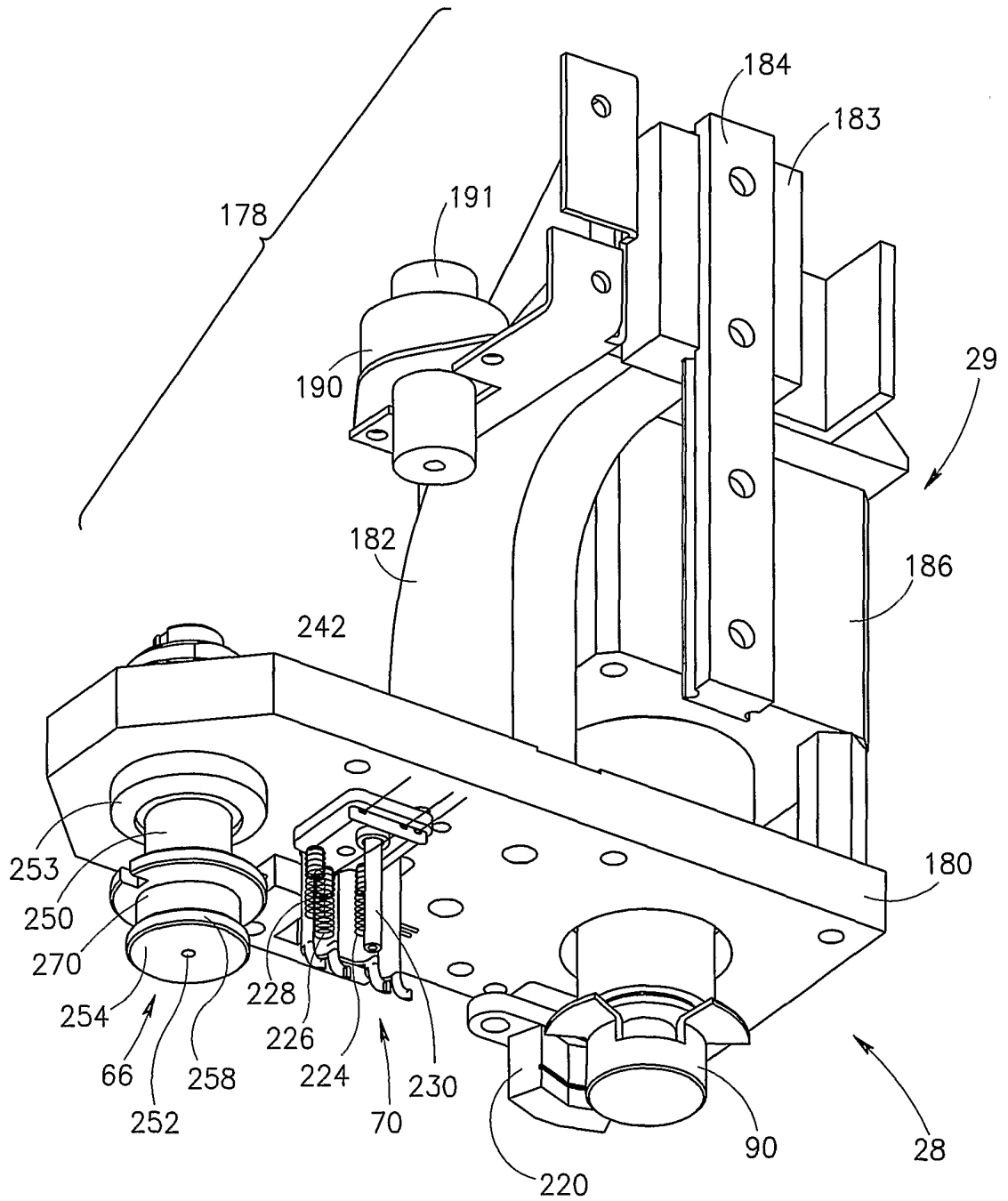


FIG.5B

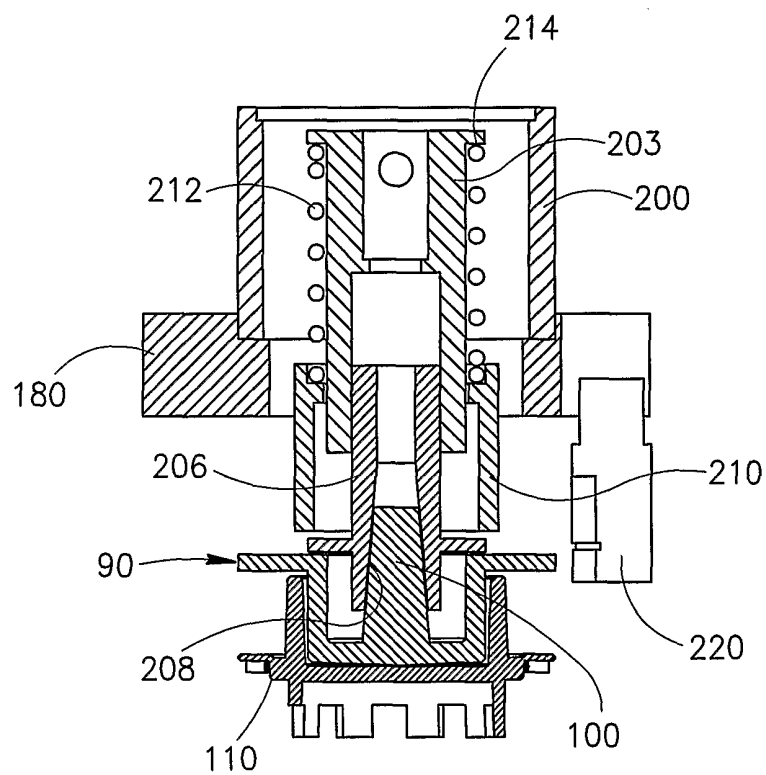
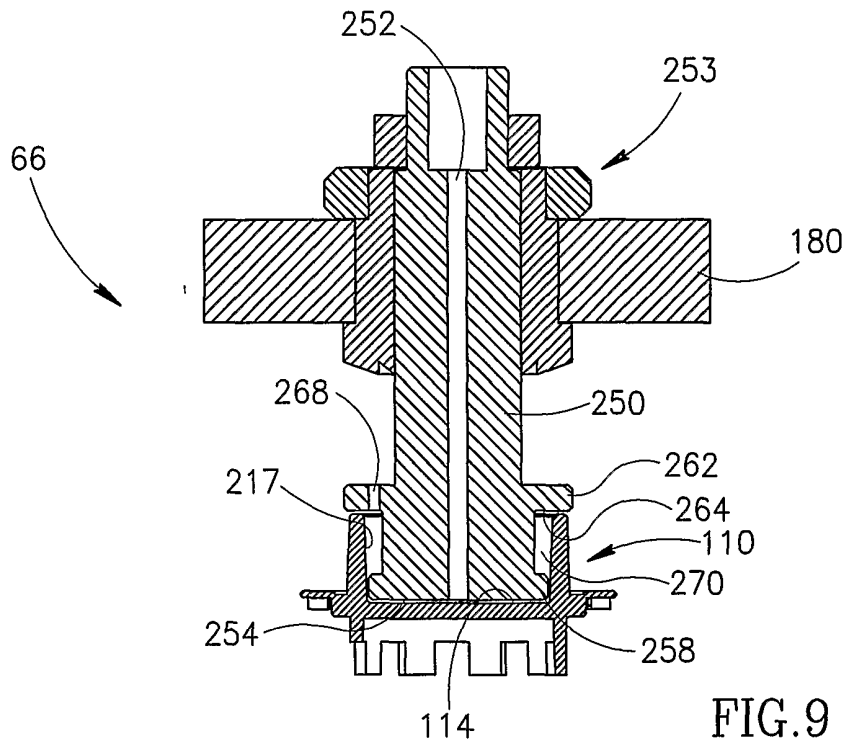
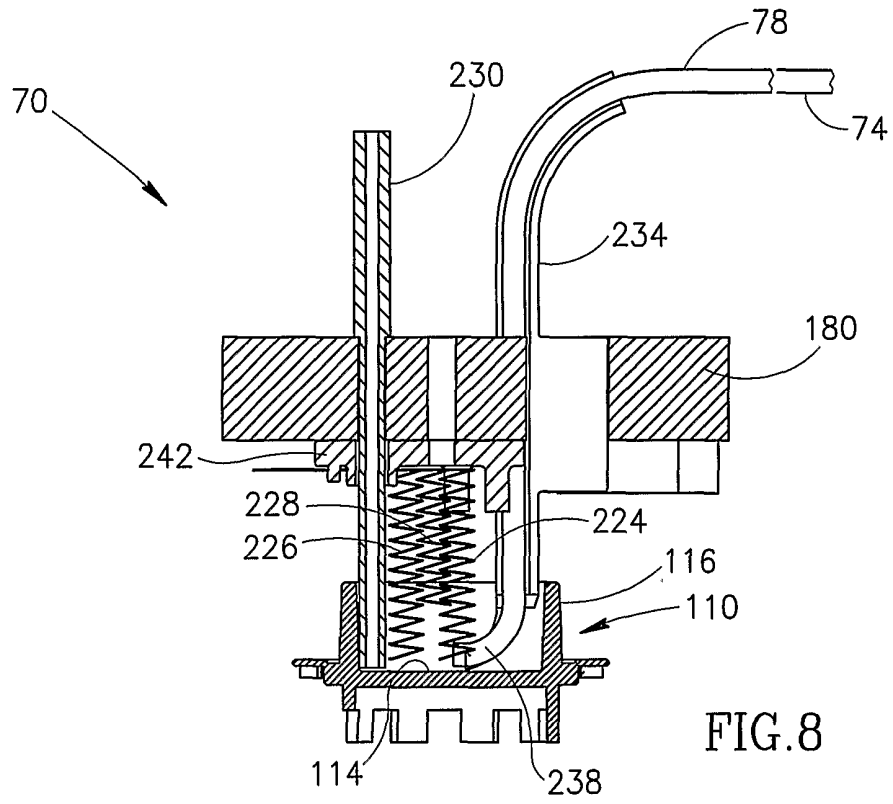


FIG. 7

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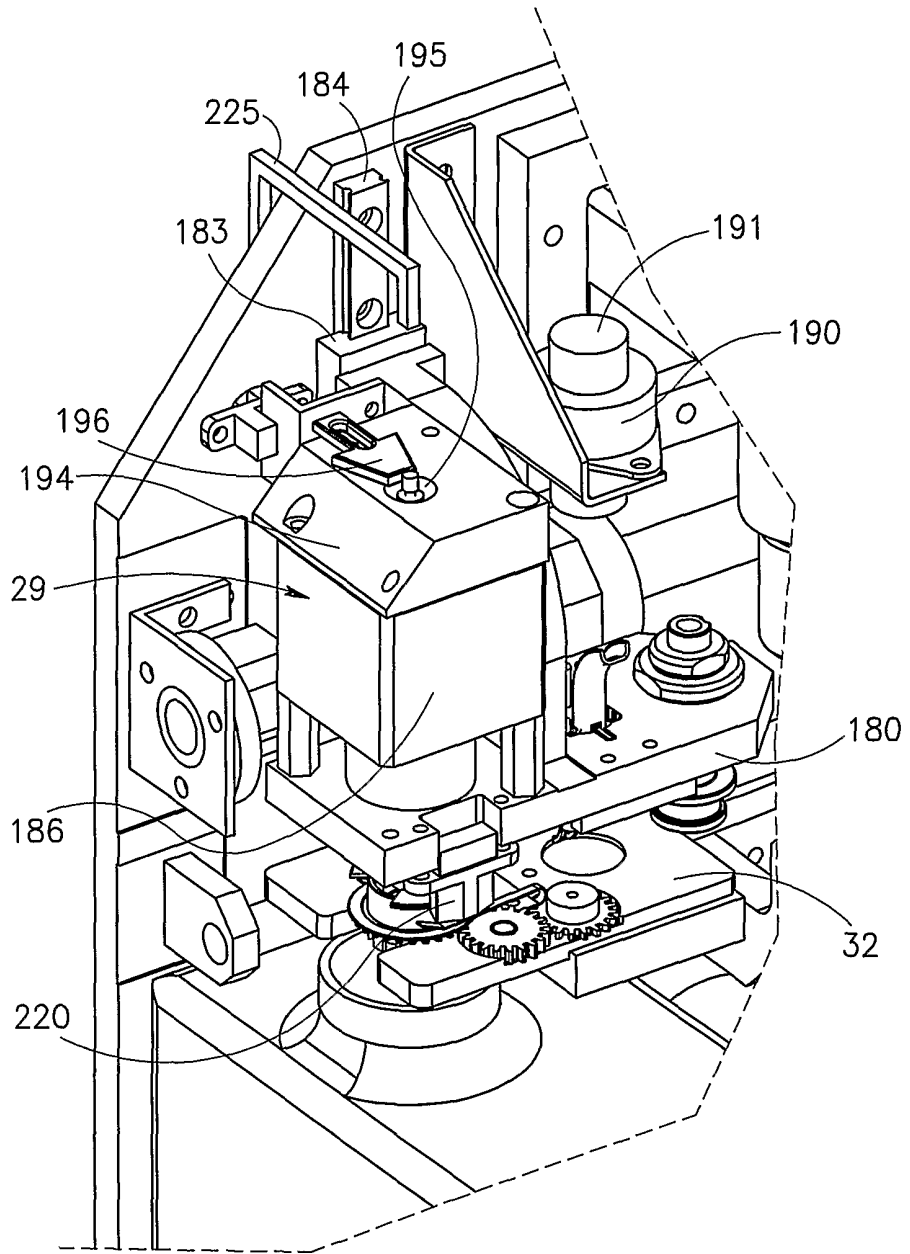


FIG.10B

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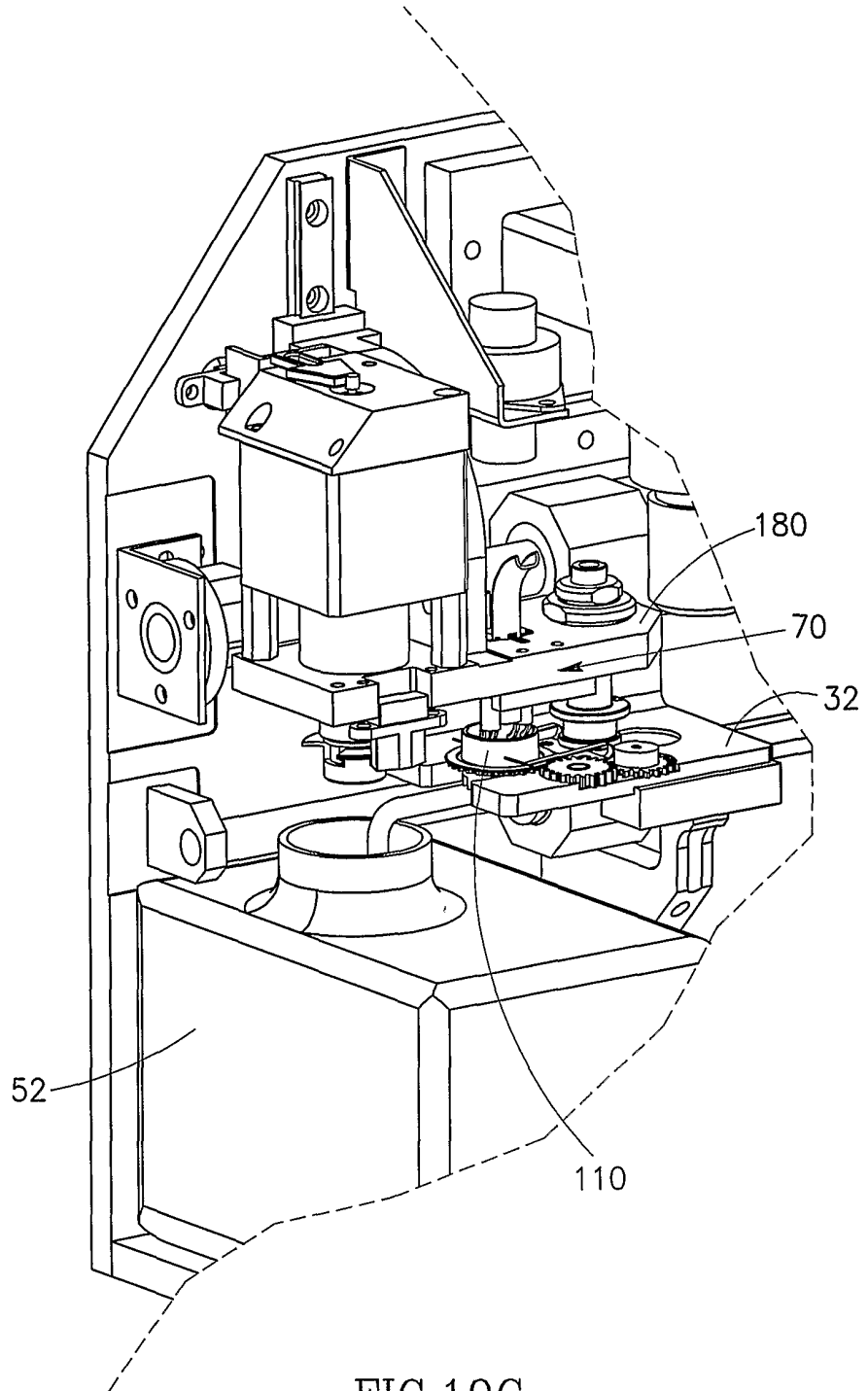


FIG.10C

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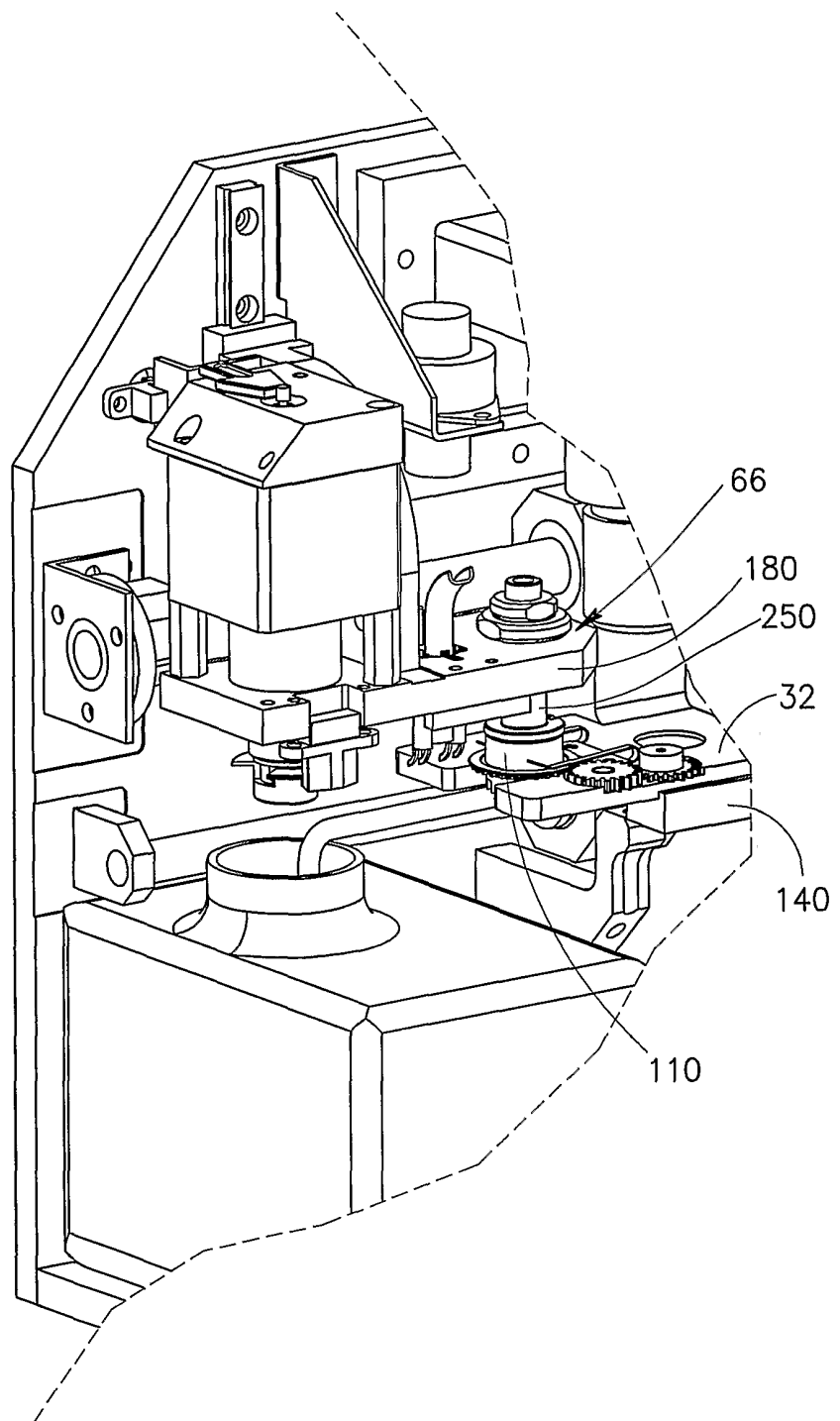


FIG.10D

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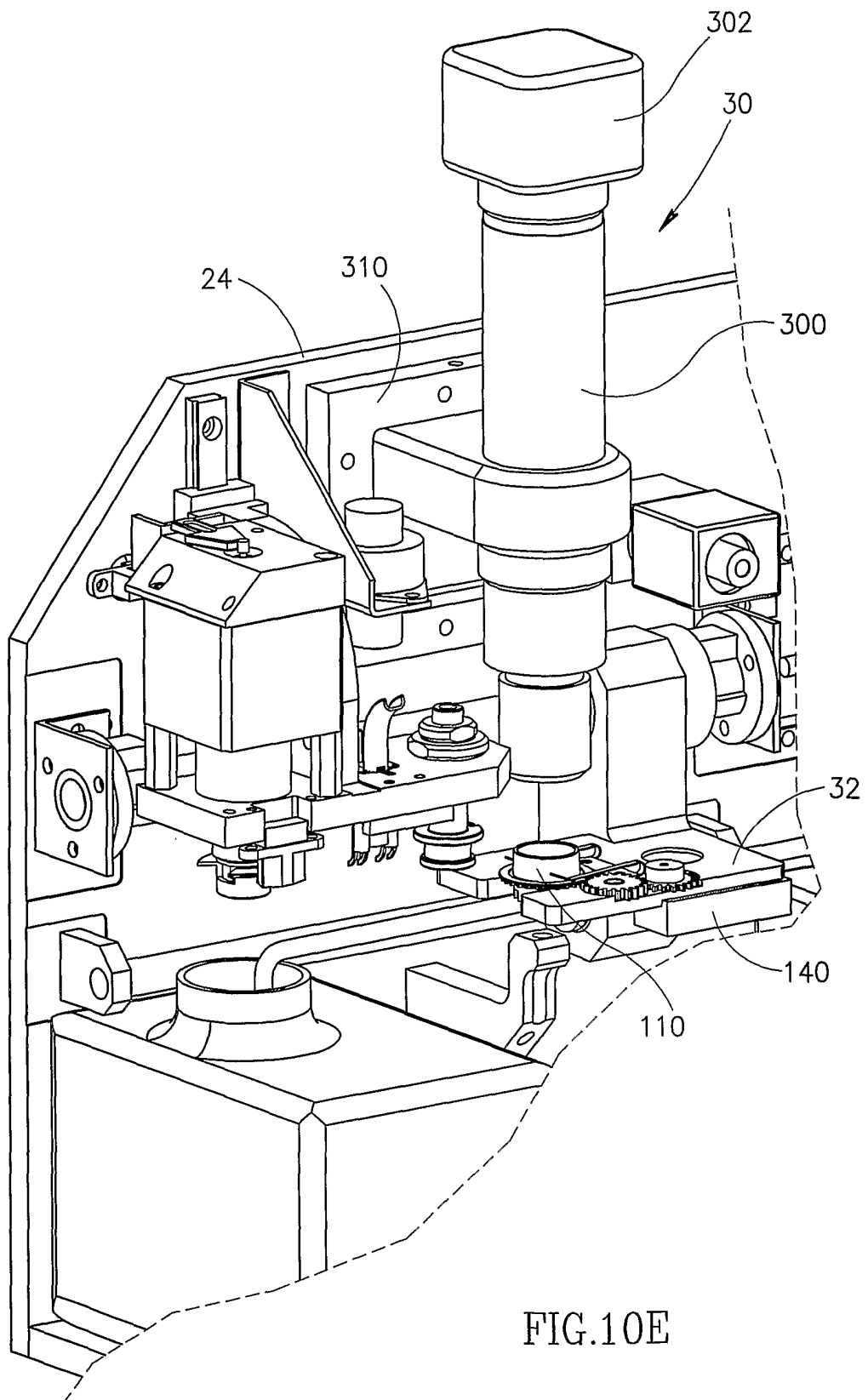


FIG.10E

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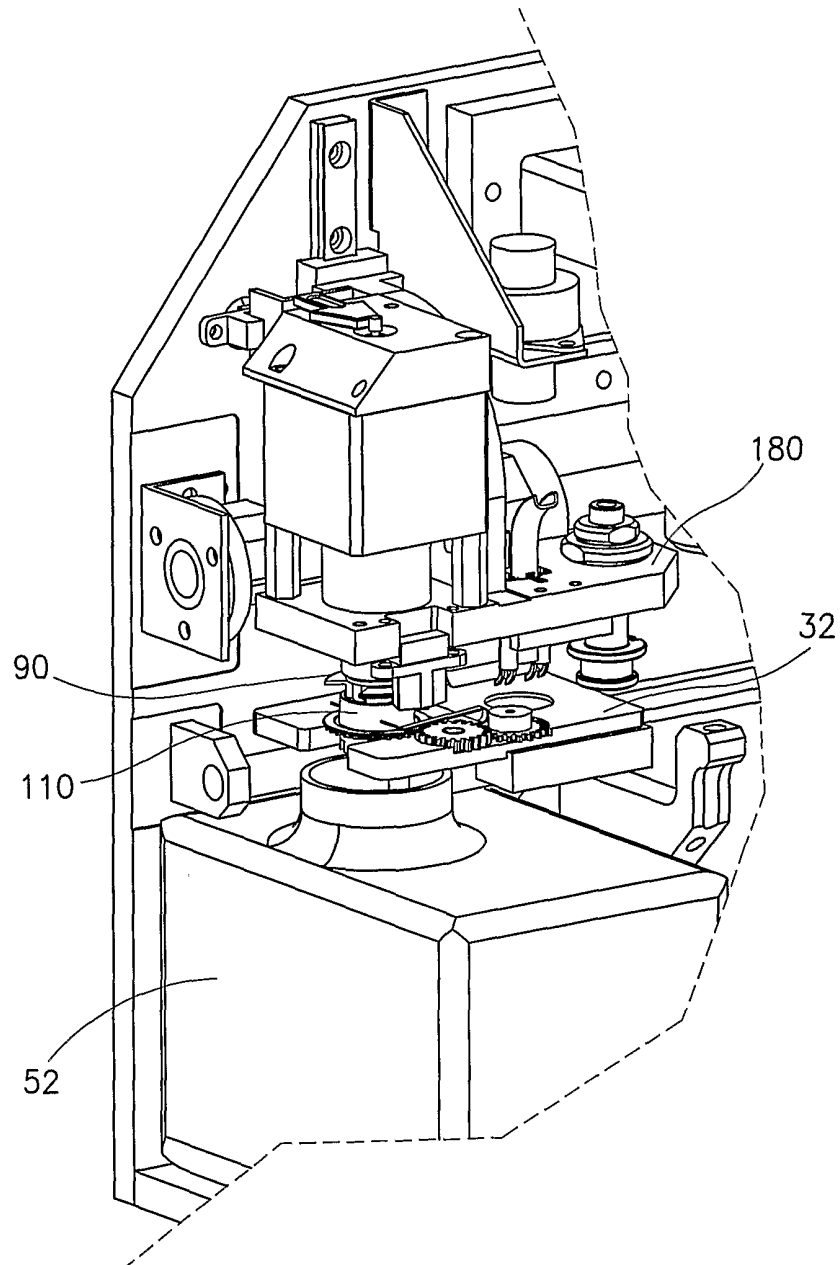


FIG.11A

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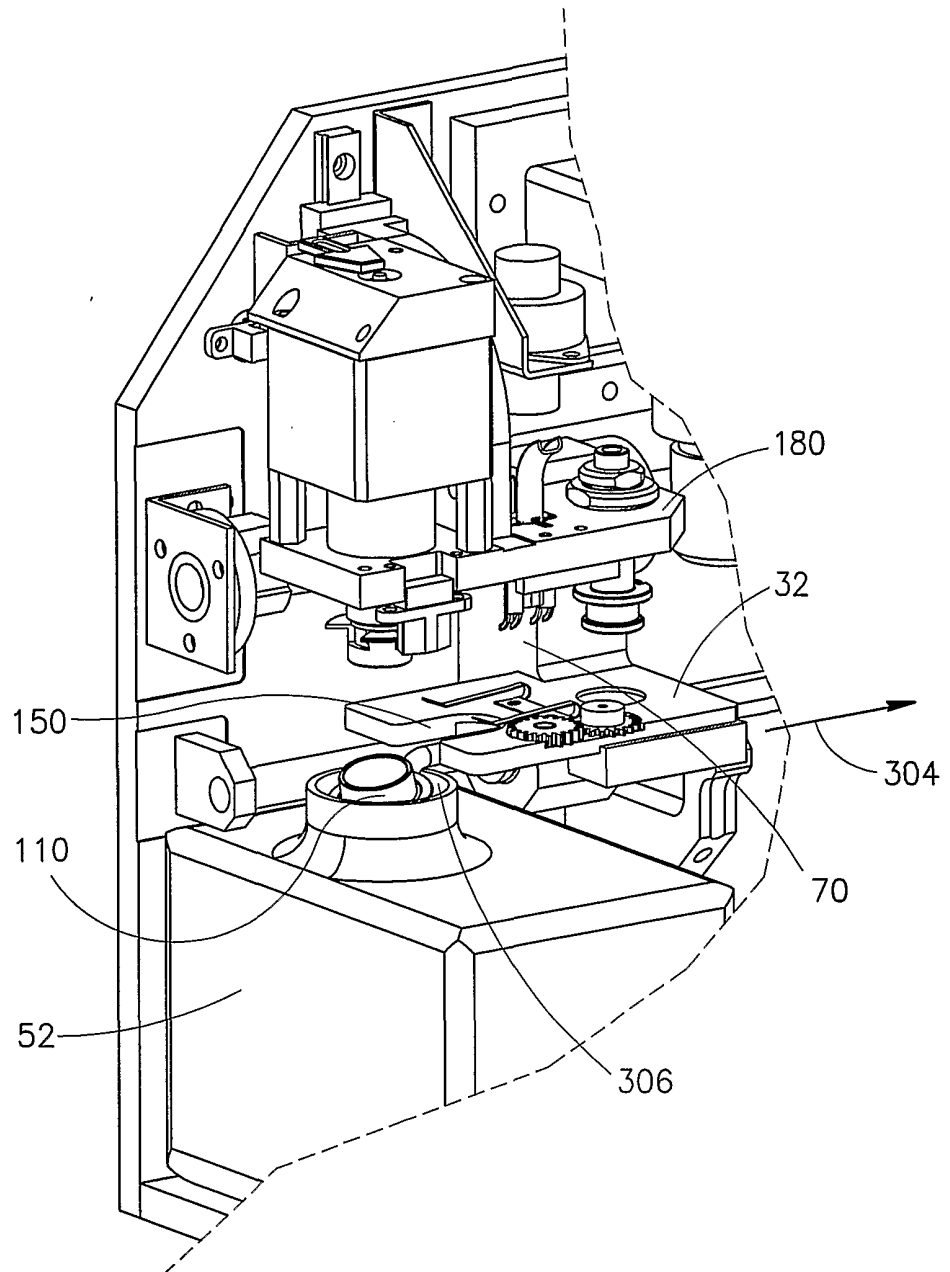


FIG.11B

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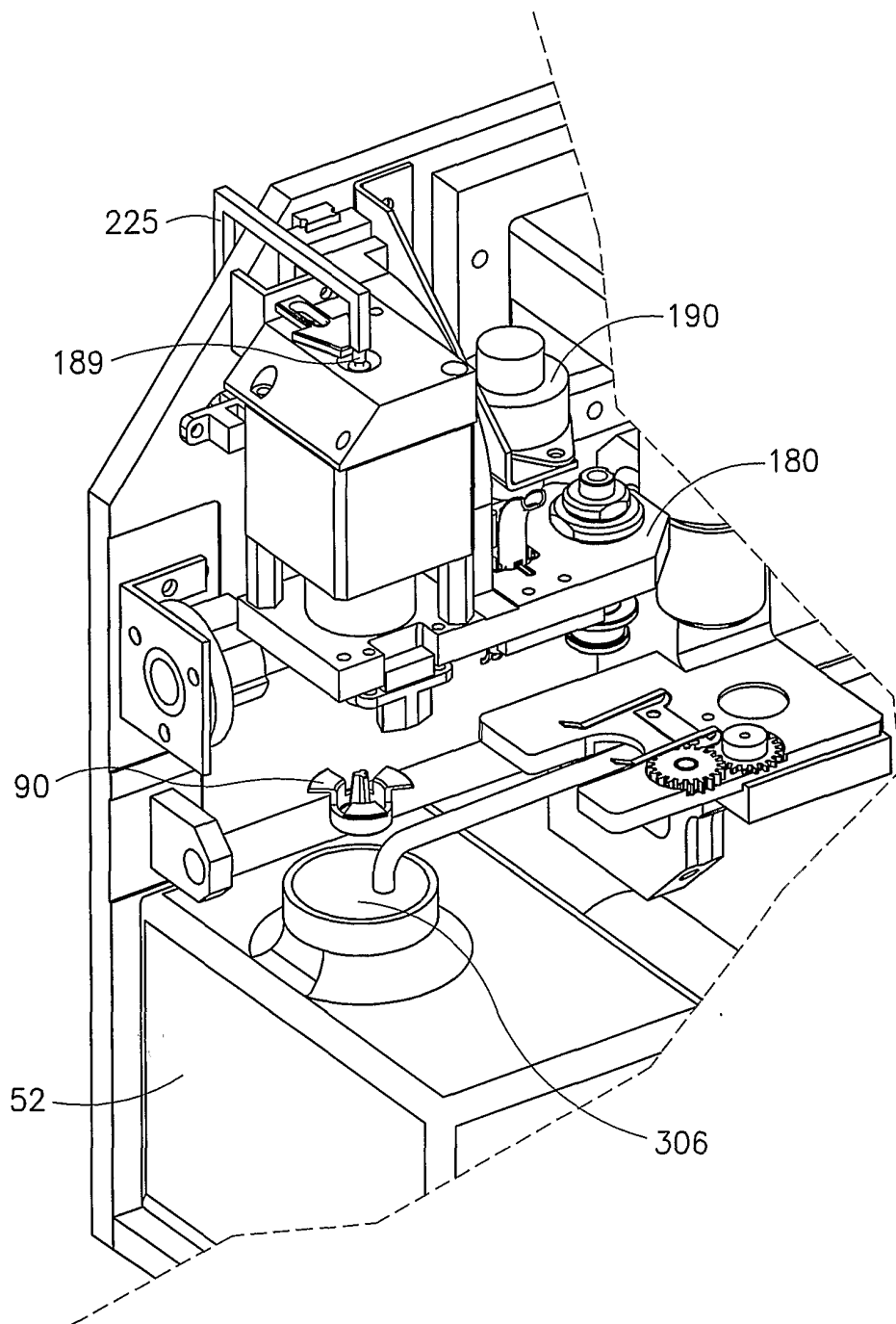


FIG.11C