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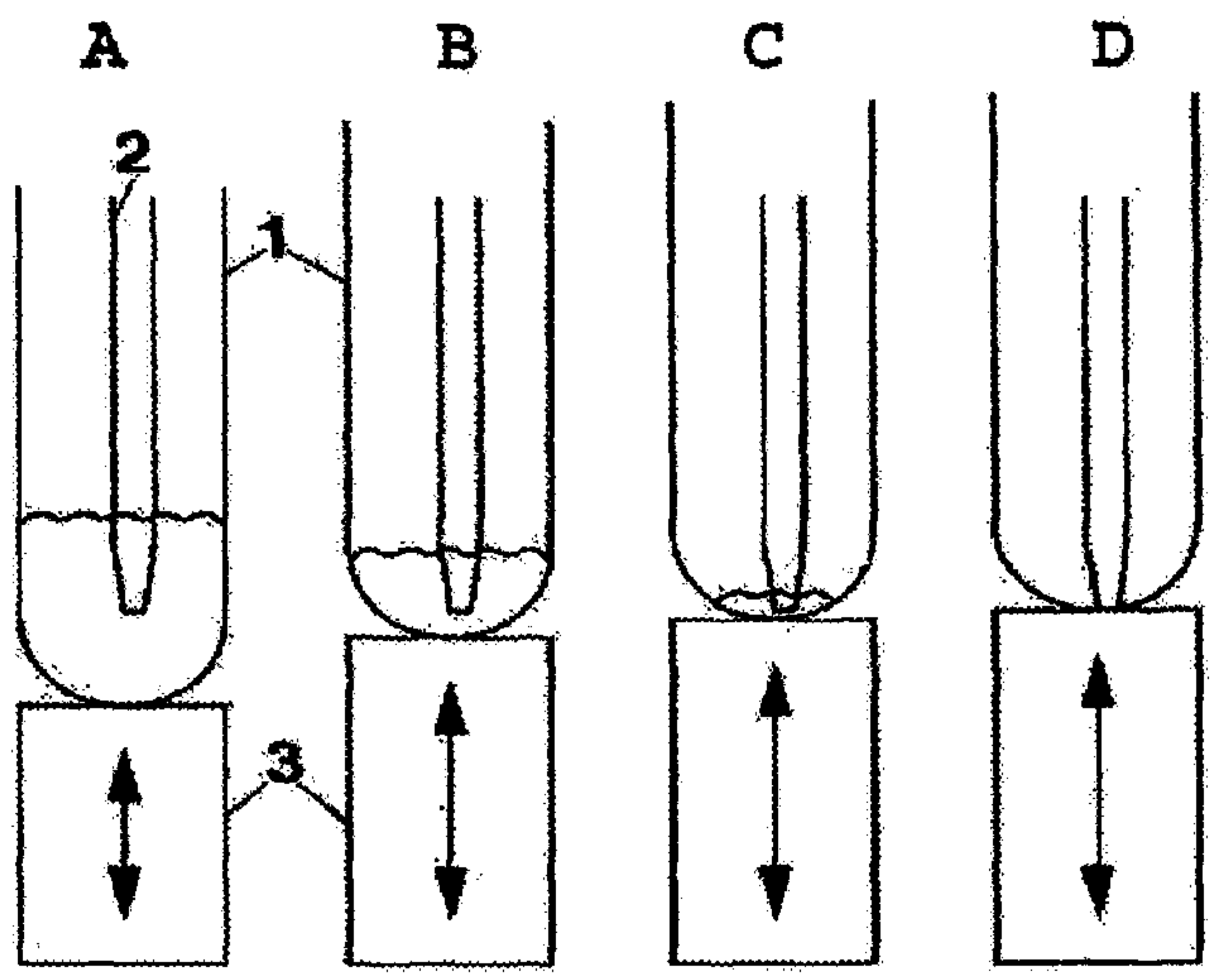
(54) Titre : DISPOSITIF ET PROCEDE DE COLLECTE INTEGRALE DE LIQUIDES A PARTIR DE RECIPIENTS
(54) Title: APPARATUS AND METHOD FOR REMAINDER-LESS UPTAKE OF LIQUIDS FROM VESSELS



(57) Abrégé/Abstract:
Apparatus for remainder-less uptake of liquids from vessels using removal units with removal tips, wherein the removal tips or the vessel bottoms are configured or arranged relative to one another such that the surface area of a vessel bottom, on which the respective removal tip would touch down when the respective removal tip is inserted into the vessel, and the end surfaces of said removal tips are tilted towards one another at least on a partial piece of the two surface areas, that is to say are not parallel there.

ABSTRACT

Apparatus for remainder-less uptake of liquids from vessels using removal units with removal tips, wherein the removal tips or the vessel bottoms are configured or arranged relative to one another such that the surface area of a vessel bottom, on which the respective removal tip would touch down when the respective removal tip is inserted into the vessel, and the end surfaces of said removal tips are tilted towards one another at least on a partial piece of the two surface areas, that is to say are not parallel there.

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Apparatus and Method for Remainder-Less Uptake of Liquids from Vessels

The present invention relates to a device and a method for the complete uptake of liquids from vessels, more particularly, for removing reagents from reaction vessels using pipettes.

Especially with applications in the field of laboratory analysis, different processes are often combined. In such cases, special vessels are used, inter alia, for receiving liquids, these liquids being removed again in the course of the application.

Because of the progressing automation, robotic systems (e.g. liquid handling automata) are being increasingly employed to transfer a sample extract from one vessel of a first process to a corresponding container for a second process, for example.

These systems for liquid transfer mostly include removal units (e.g. pipettes) that are lowered from above into the vessels, which are, as a rule, upright, and suck the liquid out of the vessels.

The removal units include a removal tip that is immersed in the liquid in order to remove the liquid. This tip is shaped such that a channel, through which the liquid is able to flow, is surrounded by a wall. The channel begins at the removal tip and extends through the removal unit.

When there is an underpressure in the channel, the liquid is sucked out of the vessel. In this way the liquid is removed.
The removal tip has an end surface at its end which is defined by the confining wall.

A disadvantage of these existing systems for liquid transfer is that the liquid cannot be removed from the vessels with no, or at least almost no, liquid remaining therein. For this reason, it is currently not possible to remove, in particular, small amounts of liquid from the vessels, or this can be achieved only with great difficulty.

The reason for this is that there must always remain a certain residual volume in the vessel since, when attempting to quantitatively transfer the liquid there is a risk of an air- and liquid-tight seal forming between the removal tip of a removal unit and the vessel bottom due to too low positioning of the removal unit. For example, a pipetting tip, as a rule, must not touch the bottom of the vessel, since on drawing up the liquid, an underpressure is formed which suctions the pipetting tip to the vessel bottom, and uptake of liquid is initially impossible as said liquid is not able to enter the pipetting tip.

By the subsequent upward movement of the pipetting tip, while the underpressure persists, the connection to the vessel bottom is released and the liquid shoots up into the tip in an uncontrolled manner. In the process, the liquid is in most cases sucked in up to the filter, which makes subsequent controlled dispensing impossible.

The existing problem is made worse by the variances with respect to dimensioning and shape of the plastics materials (pipetting tips, vessels). For high-sensitivity applications in the field of PCR-based analysis, an automated quantitative transfer of small volumes of liquid is necessary since all previous measures lead to sensitivity losses or total loss.

The object of the present invention was to provide a device and a method which overcome the above-mentioned disadvantages and which are suited for a complete uptake of liquids from vessels.

This object is achieved with the device and the method according to the claims.

According to the claims, the device for the complete uptake of liquids comprises a removal unit with a removal tip, and a vessel containing the liquid to be removed, wherein the removal tip or the vessel bottom are configured or arranged relative to each other such that that area of the surface of the vessel bottom on which the removal tip would touch down when said removal tip is inserted into the vessel, and the end surface of the removal tip are tilted relative to each other at least in a portion of the two surface areas, that is to say are not parallel there.
In this way, even if the removal tip touches down on the vessel bottom there will always result a gap between the corresponding area of the bottom and the end surface of the removal tip, so that the removal tip is prevented from suctioning to the bottom. In this case, the liquid is able to flow through the gap into the removal unit.

Preferred arrangements or shapes, either alone or in combination with one another, are:
- the bottom of the vessel is positioned so as to be oblique relative to the end surface of the removal tip;

- the bottom of the vessel is curved, said removal tip being arranged eccentrically to the apex of the curvature;

- the end surface of the removal tip is bevelled relative to the longitudinal axis of the removal tip or has another shape that deviates from the plane surface, such as, for example, the shape of a crown, or slots are incorporated in the otherwise plane end surface.

If the vessel is curved at its bottom end, it is advantageous, for example, to position the vessel below the removal unit in such a way that the tip of the removal unit would touch the bottom of the vessel at a small distance, i.e. 1/5th - 1/100th of the vessel diameter, from the apex of the curvature.

One preferred embodiment comprises, in addition, at least one compensation element which is suited for ensuring that if the removal tip touches the vessel bottom when the removal tip is being inserted into the vessel, the vessel or the removal tip can perform an evasive movement in the direction of the relative direction of movement of the removal tip and vessel.

This is the case, for example, if the vessel and/or the removal tip are resiliently supported.

Preferred compensation elements are active or passive elements or combinations of active and passive elements.

Preferred passive elements are springs or other resilient materials, such as resilient plastics, for example foamed plastics or rubber. Springs suitable for use are, in particular, helical or leaf springs.

The passive elements are advantageous in that compensation of the pressure acting on the vessel bottom and the removal tip is accomplished easily and without additional control. When the removal tip touches down on the vessel bottom, the latter automatically, by action of the elastic compensation element, performs an evasive downward movement, or the removal tip performs an evasive upward movement.

Preferred active elements are piezo elements, muscle wires or motors, which, preferably each fitted with mechanics, effect a compensation of the pressure when the removal tip touches the vessel bottom.

In one preferred embodiment, these active elements are provided with a sensor, which measures the contact pressure, and with control electronics controlling the deflection of the compensation element.

Active control of the pressure between the removal tip and the vessel bottom is advantageous in that failures, such as tilting, can be compensated.

In one preferred embodiment, the compensation elements are made up of commercially available resilient material. A compensation element, in particular, comprises elastic plastics or springs.

In one preferred embodiment, the vessel is arranged on the compensation element, preferably in a vertical or slightly tilted position, the vessel preferably being retained by a holding device which is fitted on the compensation element.

The vessel may be connected to the compensation element or the holding device either detachably or non-detachably. A detachable connection has the advantage that the vessel can be readily replaced and that, for example, disposable vessels can be used.

Preferably, the vessel on the compensation element or on the holding device is merely placed thereon.

In the case of the first preferred embodiment, the compensation element is preferably mounted on a base plate to ensure that the element stands safely.

In a further preferred embodiment, the compensation element is arranged directly in or on the removal unit, so that the complete removal unit is elastically mounted, or a part of the wall of the removal unit is made of an elastic material or is configured as a bellows, so that at least the removal tip is elastically mounted.

In another preferred embodiment, compensation elements are arranged both on the vessel and on the removal unit.

To avoid tilting, the compensation element is preferably arranged in a guide unit, such as, for example, a sleeve which has at least one opening at its top side. This guide unit has guide elements that guide the compensation element, the holding device, the vessel or the removal unit along a straight path. Preferably, the walls of the above-mentioned sleeve form the guide elements.

The length of the guide unit is such that it may receive the compensation element, preferably along with the holding device, and, especially preferably, also receive at least part of the vessel or of the removal unit.

The removal unit is preferably fixedly attached to the base plate; in particular, the guide unit is screwed on the base plate with a thread.

In yet another preferred embodiment, the compensation element is configured as a distance adjustment element which is suited for changing the relative vertical distance between the vessel bottom and the tip of the removal unit as a function of the amount of liquid in the vessel when a liquid is being taken up from a vessel by a removal unit, in such a way that as an increasing amount of liquid is removed the distance between the vessel bottom and the tip of the removal unit decreases.

The tip of the removal unit should always remain below the level of the liquid during removal, to prevent air from being sucked in.

With a liquid-filled vessel into which a removal unit is being inserted, the removal process, in this case, is as follows:
In the filled state of the vessel, the distance between the vessel bottom and the tip of the removal unit is adjusted by the distance adjustment element so as to be at its maximum.

The removal unit removes liquid from the vessel. Because of this removal of liquid, the removal unit will become heavier, as a function of the amount of liquid, and the vessel will become lighter. In addition, the liquid level will rise in the removal unit, and it will drop in the vessel.

As the removal unit continues to remove liquid, this distance is continuously reduced by the distance adjustment element, as a function of the amount of liquid taken up. During this process, the tip of the removal unit should always lie below the liquid level in the vessel.

As a measure for the removed liquid, on the one hand, the weight force of the liquid that has been taken up or which has remained in the vessel may be used, or, on the other hand, the liquid level in the vessel or in the removal unit.

The tip of the removal unit should not touch the vessel bottom, or at least not before the liquid has been almost completely sucked up.

Preferred distance adjustment elements are active or passive elements, or combinations of active and passive elements.

Suitable passive elements regulate the distance between the vessel bottom and the tip of the removal unit, preferably via the weight force of the amount of liquid contained in the vessel.

With passive distance adjustment elements, regulation of the distance between the vessel bottom and the tip of the removal unit is automatically effected due to the always differing weight force of the amount of liquid transferred, if the distance adjustment element is arranged below the vessel or at the removal unit. The vessel becomes lighter and is automatically, by the elastic distance adjustment element, pressed upwards, or the removal unit becomes heavier and automatically advances downwards.

Suitable active elements preferably regulate the distance between the vessel bottom and the tip of the removal unit via the weight force of the amount of liquid contained in the vessel or taken up by the removal unit, or via the liquid level thereof.

In a preferred embodiment, these elements are fitted with a sensor measuring the amount of liquid, and with control electronics controlling the deflection of the distance adjustment element.

Active distance adjustment has the advantage that failures, such as tilting, can be compensated. If the height of the liquid level in the vessel is measured by the sensor, this has the additional advantage that it is possible to simultaneously monitor whether the tip of the removal unit is in fact always below the liquid level.

Preferably, passive distance adjustment elements for inhomogeneously formed (e.g. curved at the end) vessels are configured such that the vessel is lifted in such a way that as the amount of liquid declines, the change in distance becomes continuously smaller per unit of liquid removed.

Particularly with resilient embodiments it is advantageous if the spring forces effective at the end of the process are weaker. This is achieved by providing an arrangement of springs of differing strength, or one spring with inhomogeneous deflection per weight force.

The device can be designed for one or more reaction vessels or removal units, for simultaneous or successive removal. In an advantageous embodiment, each sample vessel, or each removal unit, is individually supported in order to compensate any variances. The device is preferably adapted for reaction plates in the 12-, 24- or 96-well formats, by grid-like arrangement of a corresponding number of the devices.

The device is preferably dimensioned such that it can be used with commercially available automata (liquid handlers) or in manual operations using pipettes.

The device preferably includes calibration elements for calibrating the distance between the removal unit and the vessel bottom, preferably in a clearly defined state of the device.

In one preferred embodiment, the compensation element is integrated directly in the vessel bottom, in particular, the vessel bottom consists of a resilient material; the vessel bottom may, for example, be foamed.

Examples of the device according to the present invention are shown in the Figures.

Figure 1, in parts A to D, is a schematic representation of the constitution of the device and of the sequence of the method.
Figures 2A and 2B show examples of the device based on springs.
Figures 3A and 3B show examples of the device with holders based on springs.
Figures 4A and 4B show examples of the device with active compensation elements.

Figure 5 shows an example of a device with a compensation element on the removal unit. Figure 6 shows an example of the device with a compensation element integrated in the removal unit.
Figure 7 shows a vessel with an integrated compensation element.

In Figure 1 (A), a compensation element (3) is shown, on which is arranged a vessel (1) filled with a liquid. A pipette (2) has been inserted in the vessel to remove liquid.
In the example, the pipette is arranged in a position slightly eccentric to the apex of the vessel bottom to prevent the pipette tip from suctioning to the bottom.

In drawings 1B and 1C the compensation element simultaneously acts as a distance adjustment element. When liquid is removed from the vessel by the pipette (B), the liquid level in the vessel and the weight force exerted by the liquid on the distance adjustment element drop. The vessel is thereby becoming lighter, is pushed upwards by the distance adjustment element.

The vessel is pushed up (C) until the tip of the pipette touches down on the bottom of the vessel or, at least, is located at a very close distance above the bottom (D).

In Figure 1D the compensation element acts such that the pressure exerted on the vessel bottom by the pipette tip upon contacting the bottom, is compensated by the vessel performing a slight evasive downward movement.

In Figure 2A, the vessel (1) is placed directly on a spring or a resilient plastic as compensation element (3), the compensation element being arranged inside a sleeve (6), on a mounting unit (8).

In Figure 2B, said sleeve (6) is of a length sufficient for the vessel to be guided safely and along a straight path by means of guide elements (7). In addition, the sleeve and the mounting unit are arranged on a base plate (9).

Figures 3A and 3B correspond to the constitution in Figures 2A and 2B, except that the compensation element is borne directly on the bottom of the sleeve and that the device is held by a holding device (4).

In Figures 4A and 4B, the vessel is held by a holding device (4) which is connected to an active compensation element. The compensation element is controlled by a sensor with a control unit (5). This element (5) measures, in Figure 4A, the weight force of the vessel and, in Figure 4B, the height of the liquid level, while here simultaneously measuring the immersion depth of the pipette tip, and deflects the distance adjustment element in accordance with a given programme.

Such a programme may be a simple formula assigning a particular deflection to each weight force or each liquid level height.

Figure 5 shows a compensation element (3) to which a removal unit (pipette) is attached such that pressure acting on the removal tip from below is compensated by an evasive upward movement.

In Figure 6, a removal unit (2) is shown having a compensation element (3) integrated in a certain area of its wall. This may be realised by adapting a portion of the wall to be elastic using a two-component injection moulding method, or by configuring a portion of the wall as a bellows, as shown here.

If the underpressure in the removal unit is constant, or at least uniform, the lower part of the removal unit becomes continuously heavier because of the increasing amount of liquid taken up; the tip may therefore also be lowered automatically, that is, the compensation element acts as a distance adjustment element.

In Figure 7 a vessel (1) is shown, the bottom of which is made of a foamed material that is sealed towards the inside to ensure sufficient tightness to liquids. This foamed material must have sufficient elasticity to be able to act as a compensation element (3). Such vessels may be produced by using a two-component injection moulding process, for example.

An advantage of such vessels is that they can be inserted in already existing holders for disposable vessels.

Claims:

1. Device for taking up liquids from vessels having a curved vessel bottom, by means of removal units having removal tips which are formed such that a channel is surrounded by a wall, and which at their end have an end surface which is defined by said surrounding wall, characterised in that the removal tip or the vessel bottom is/are configured or arranged relative to each other such that that area of the surface of the vessel bottom on which the removal tip would touch down when said removal tip is inserted into the vessel, and the end surface of the removal tip are tilted relative to each other at least in a portion of the two surface areas, that is to say are not parallel there, and
that the removal tip is arranged eccentrically to an apex of the curved vessel bottom such that when the removal tip touches down on the vessel bottom there will always result a gap between the corresponding area of the bottom and the end surface of the removal tip, so that the removal tip is prevented from suctioning to the bottom and the liquid flows through the gap into the removal unit.

2. Device according to claim 1, characterised in that the bottom of the vessel is positioned so as to be oblique relative to the end surface of the removal tip.

3. Device according to claim 1 or 2, characterized in that the end surface of the removal tip has a shape deviating from the plane surface.

4. Device according to claim 3, characterized in that the end surface of the removal tip is bevelled relative to the longitudinal axis of the removal tip.

5. Device according to any one of claims 1 to 4, characterised in that the device includes at least one compensation element which is suited to ensure that when the removal tip touches the vessel bottom, the vessel or the removal tip can perform an evasive movement in the direction of the relative direction of movement of the removal tip and vessel.

6. Device according to claim 5, characterised in that the compensation element is arranged in a guide unit.

7. Device according to claim 6, characterized in that the guide unit comprises guide elements that guide the compensation element, the holding device, the vessel or the removal unit along a straight path.

8. Device according to claim 6 or 7, characterized in that said guide unit is a sleeve having at least one opening at its top side.

9. Device according to any one of claims 6 to 8, characterized in that said guide unit is a sleeve having at least one opening at its top side, and said sleeve comprises walls which form the guide elements.

10. Device according to claim 8 or 9, characterised in that the sleeve has a length which is such that the sleeve may receive the compensation element.

11. Device according to claim 8 or 9, characterized in that the sleeve has a length which is such that it may receive the compensation element with a holding device.

12. Device according to claim 10 or 11, characterized in that the length of the sleeve is such that it may receive the compensation element and also receive at least part of the vessel or of the removal unit.

13. Device according to any one of claims 5 to 12, characterised in that the compensation element comprises active or passive elements.

14. Device according to any one of claims 5 to 12, characterized in that the compensation element comprises springs and other resilient materials, piezo elements, muscle wires or motors.

15. Device according to any one of claims 5 to 14, characterised in that the compensation elements are configured as distance adjustment elements.

16. Device according to any one of claims 1 to 15, characterised in that the device comprises calibration elements to calibrate the distance between the vessel bottom and the tip of the removal unit.

17. Method for taking up a liquid from a liquid-filled vessel by means of a removal unit having a removal tip which is formed such that a channel is surrounded by a wall, and which at its end has an end surface which is defined by said surrounding wall,
the method comprising:

(a) providing said removal unit and a vessel having a curved bottom,

(b) arranging the removal tip eccentrically to an apex of the curved bottom of the vessel,

(c) inserting the removal tip into the vessel, and

(d) causing the liquid to flow into the removal unit by suction;

wherein, in step (b), said removal tip is arranged such that that area of the surface of the vessel bottom on which the removal tip touches down when said removal tip is inserted into the vessel, and the end surface of the removal tip are tilted relative to each other at least in a portion of the two surface areas, that is to say are not parallel to each other, so that when the removal tip touches down on the vessel bottom there will always result a gap between the corresponding area of the bottom and the end surface of the removal tip, so that the removal tip is prevented from suctioning to the bottom and the liquid flows through the gap into the removal unit.

FIG. 1

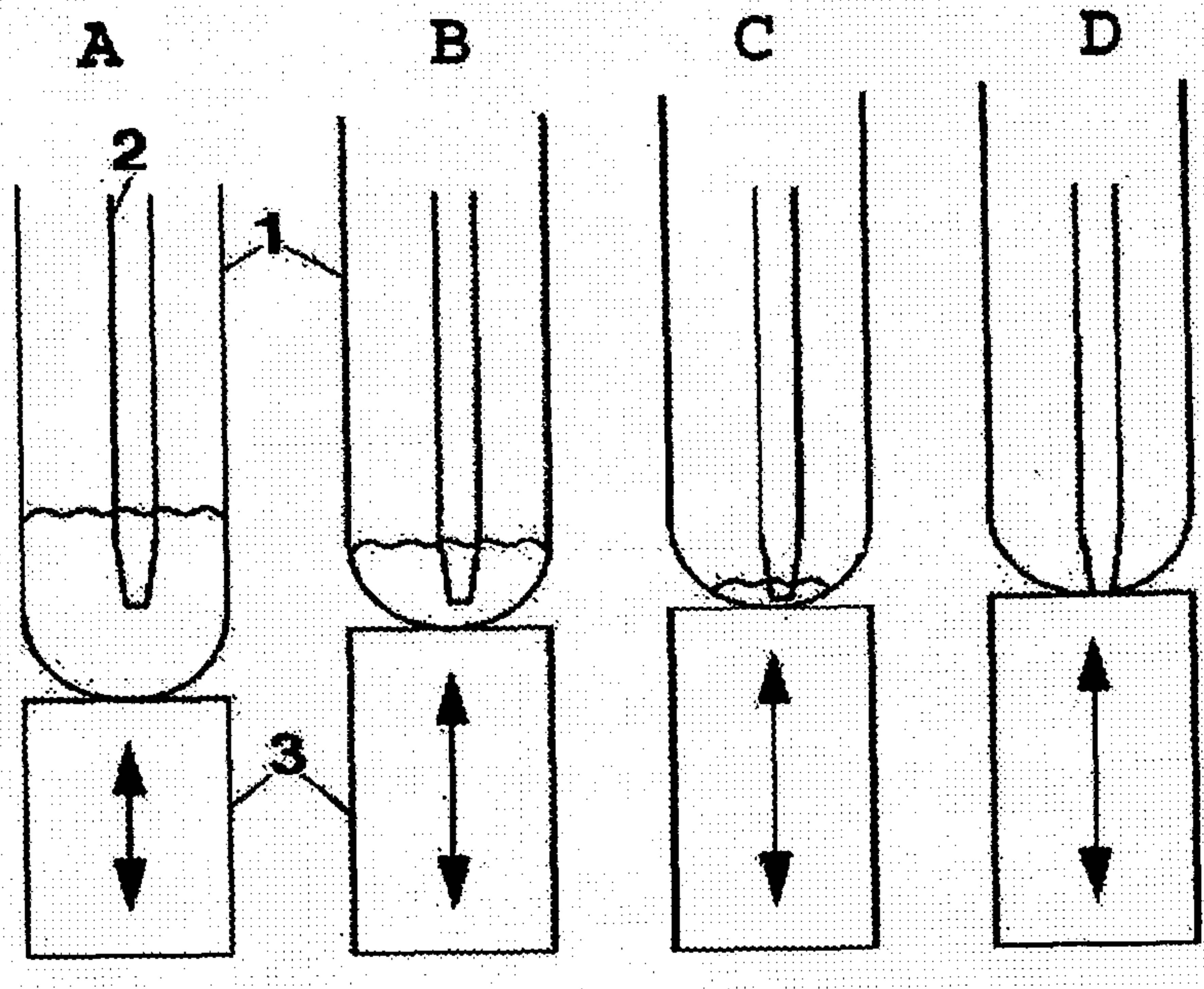


FIG. 2A

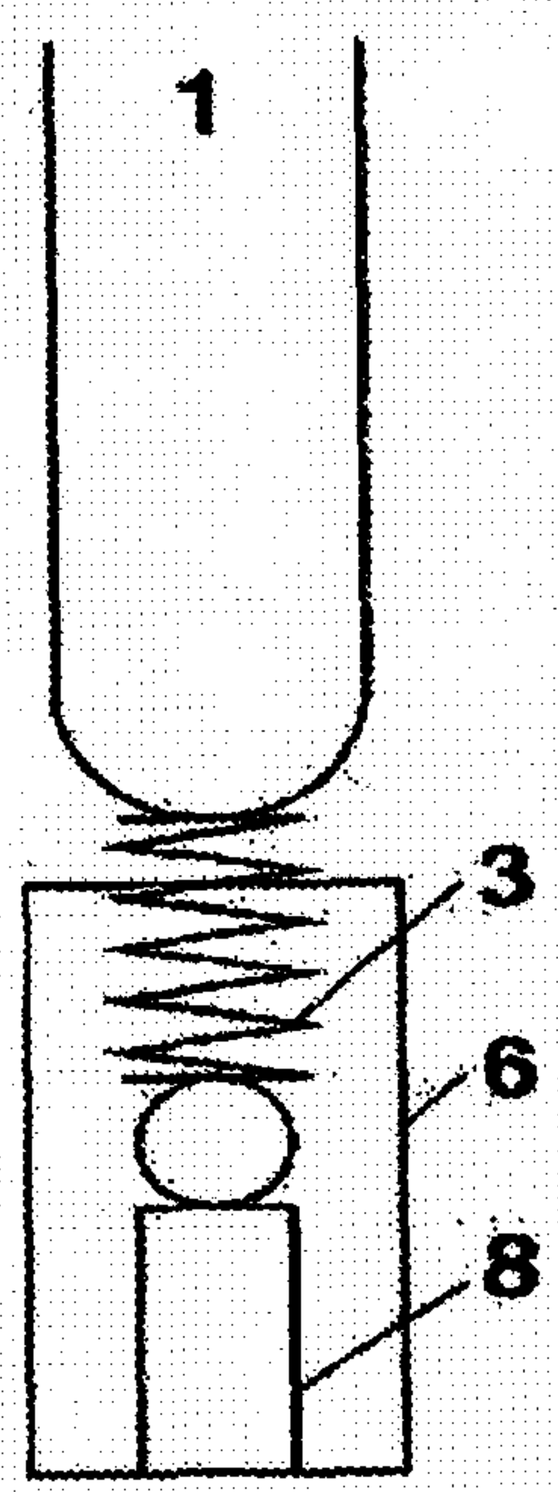


FIG. 2B

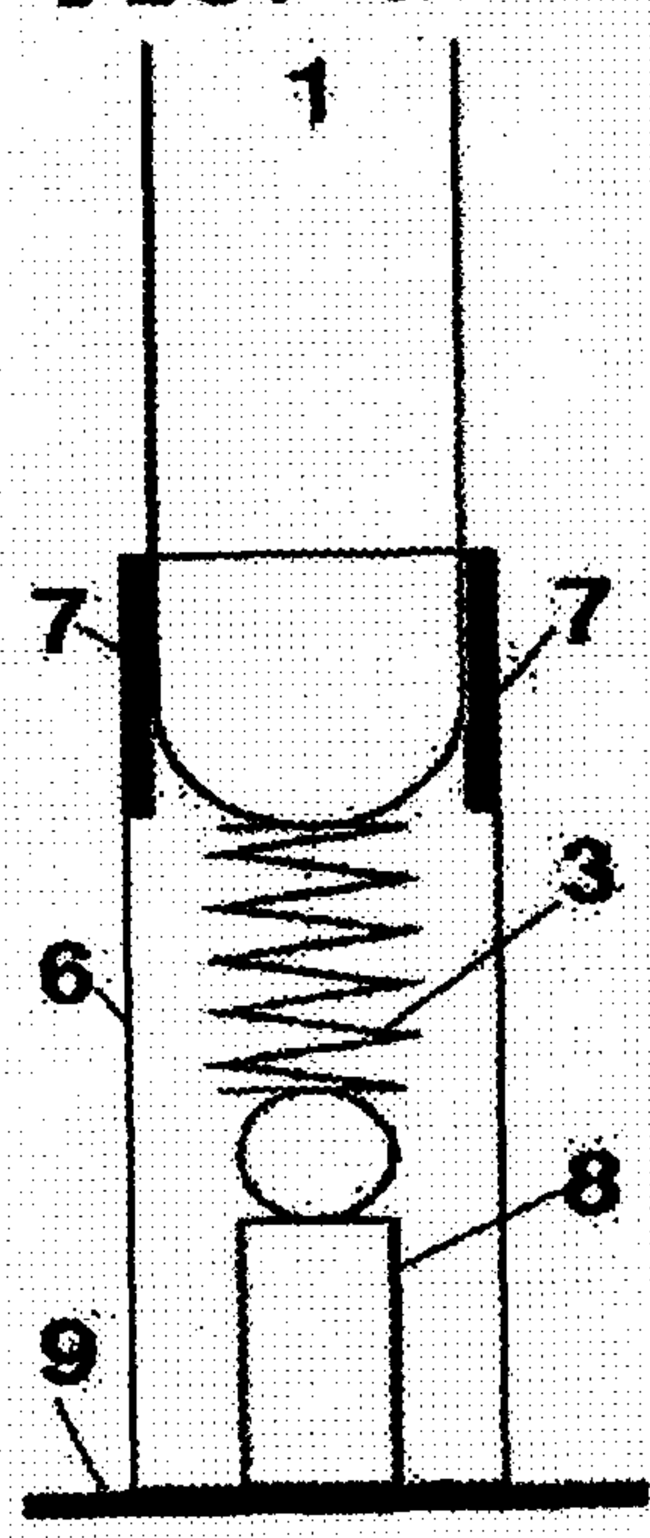


FIG. 3A

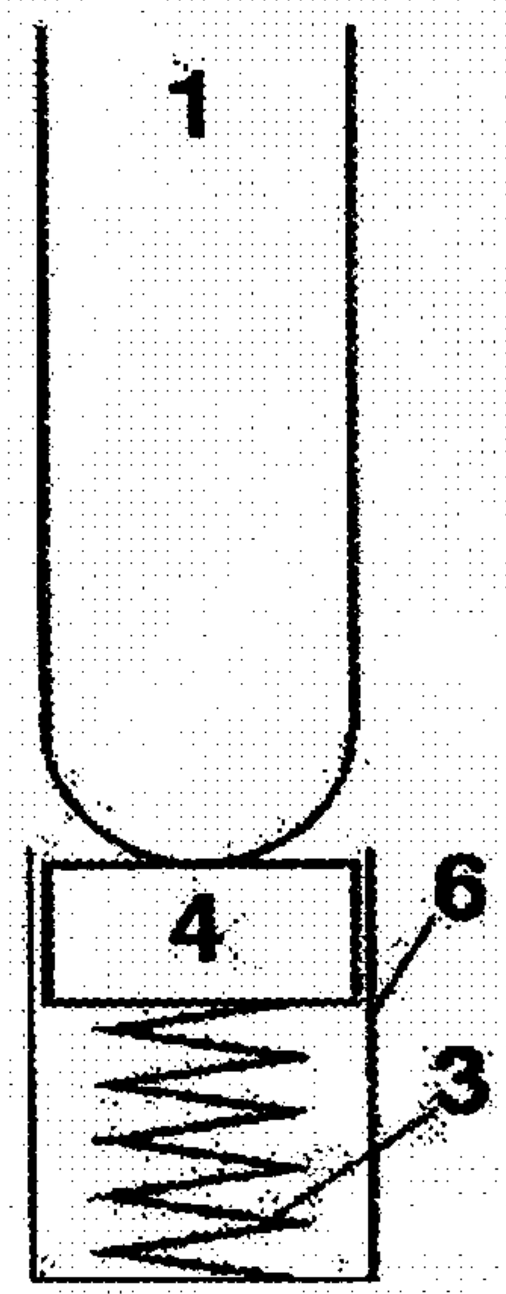


FIG. 3B

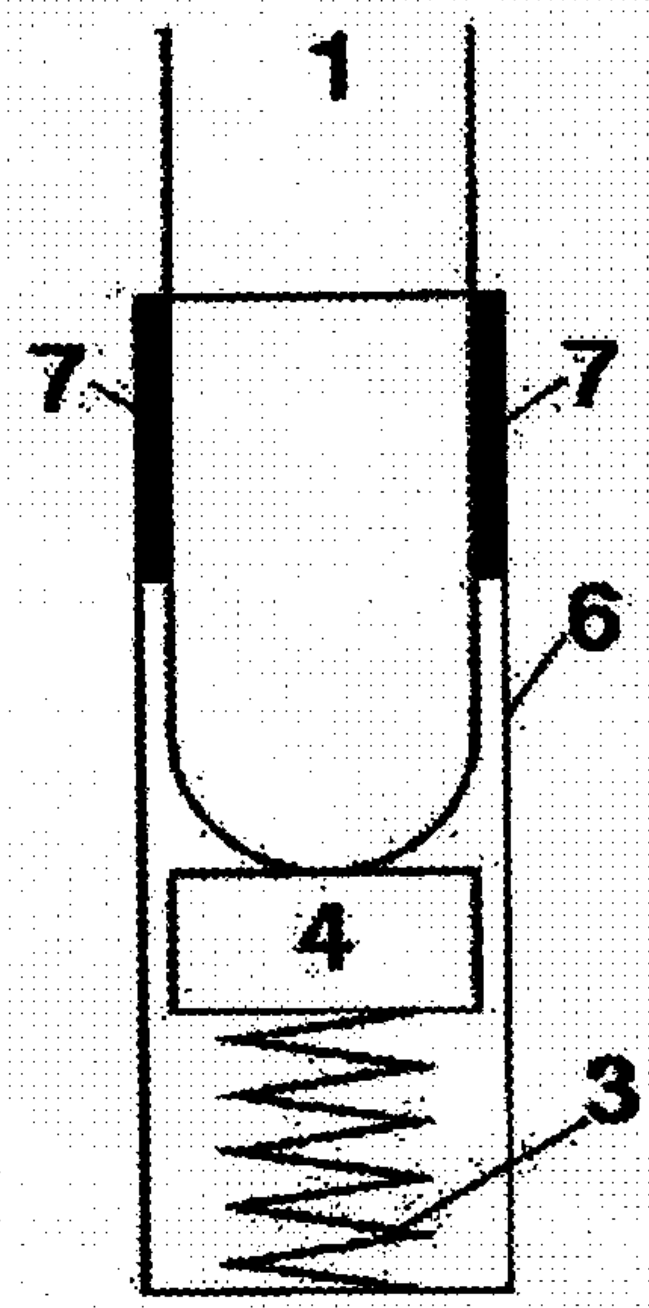


FIG. 4A

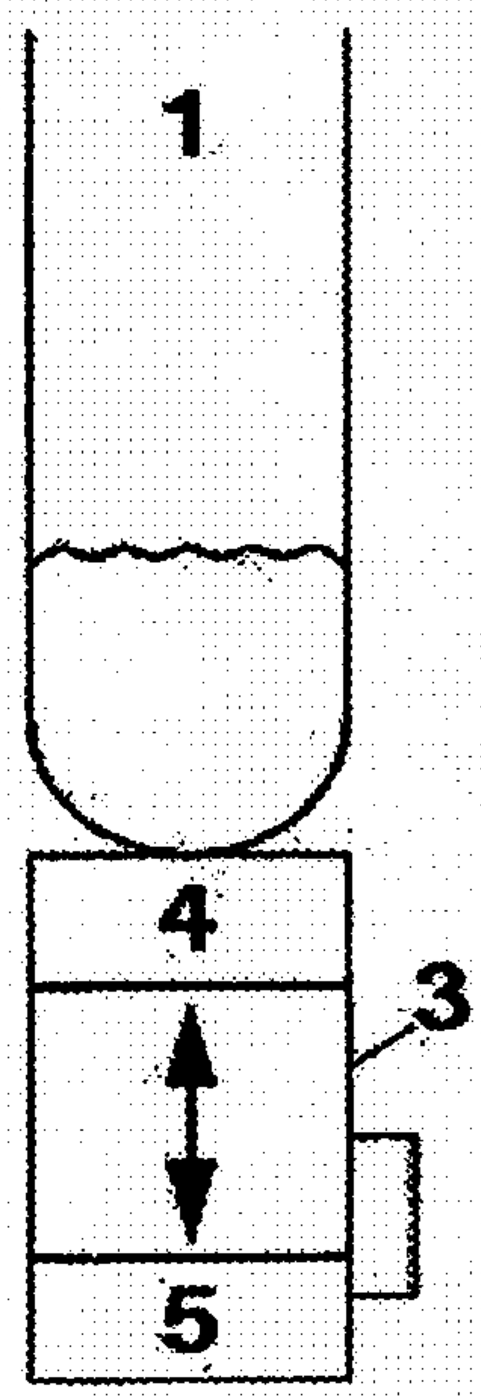


FIG. 4B

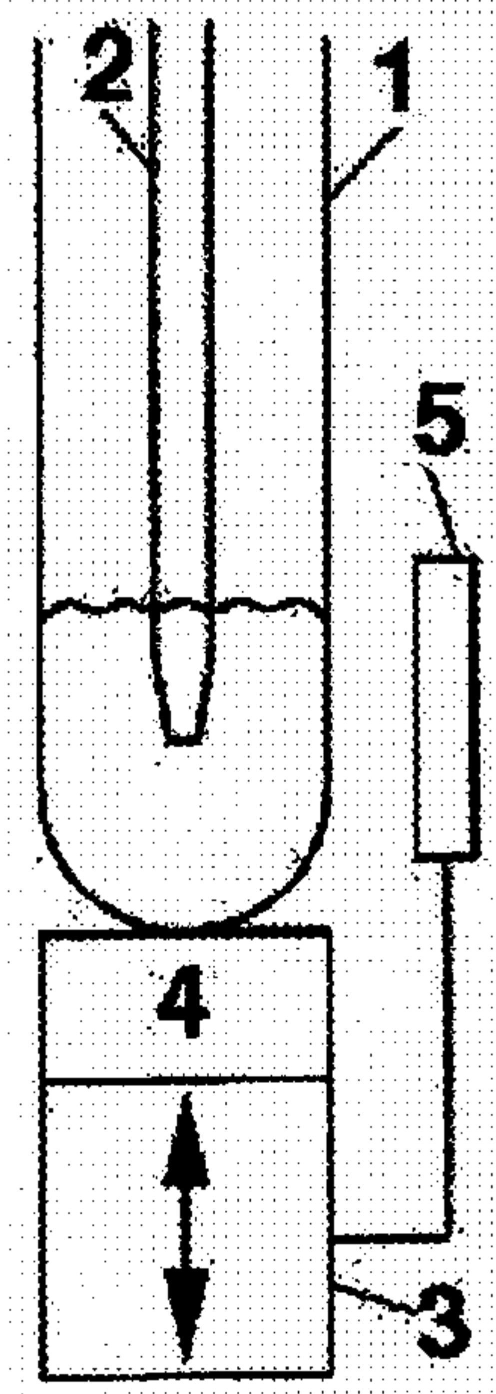


FIG. 5

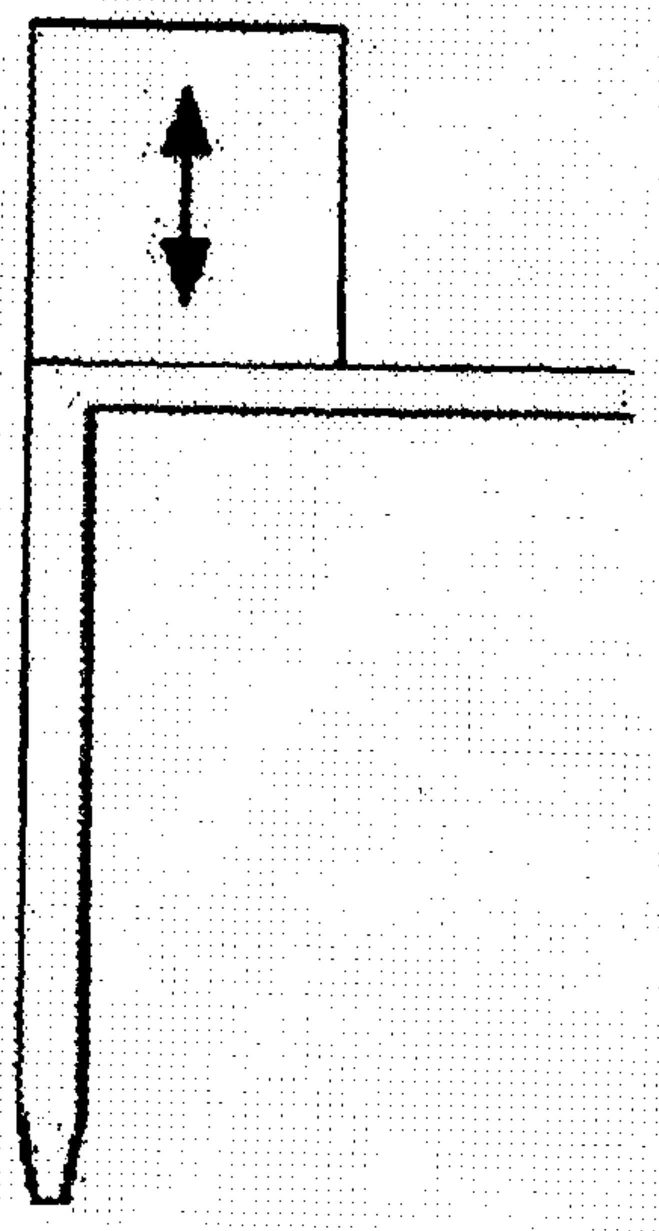


FIG. 6

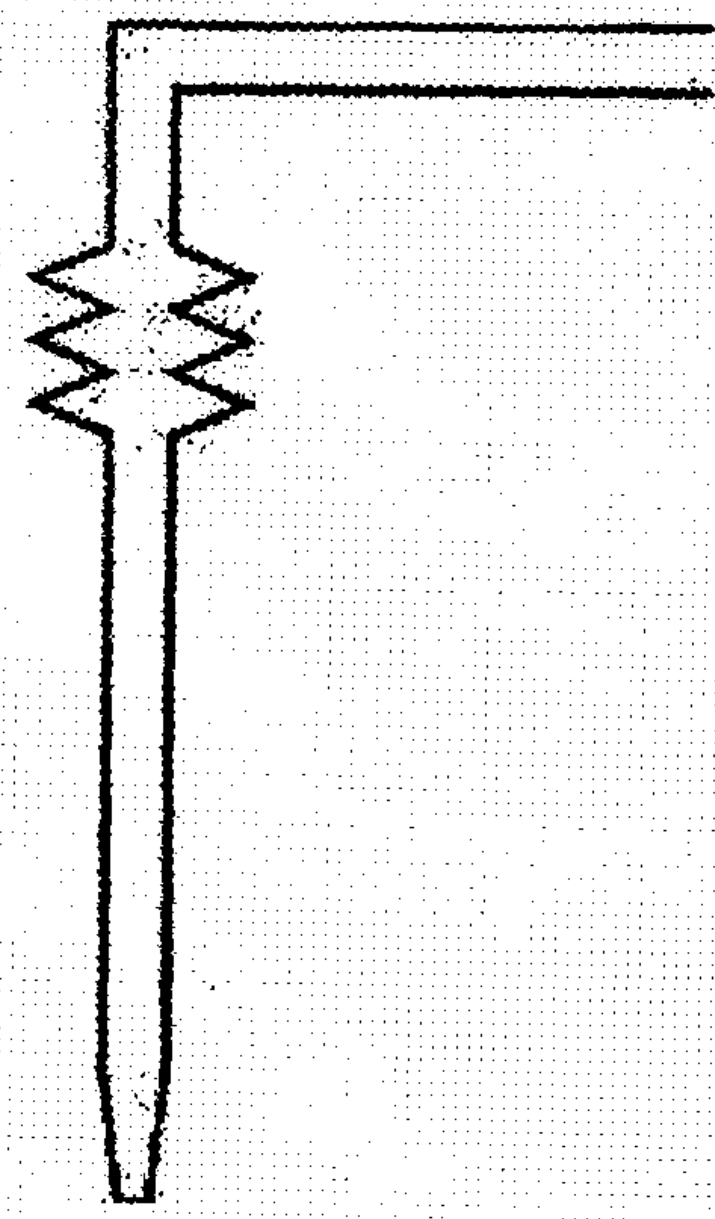
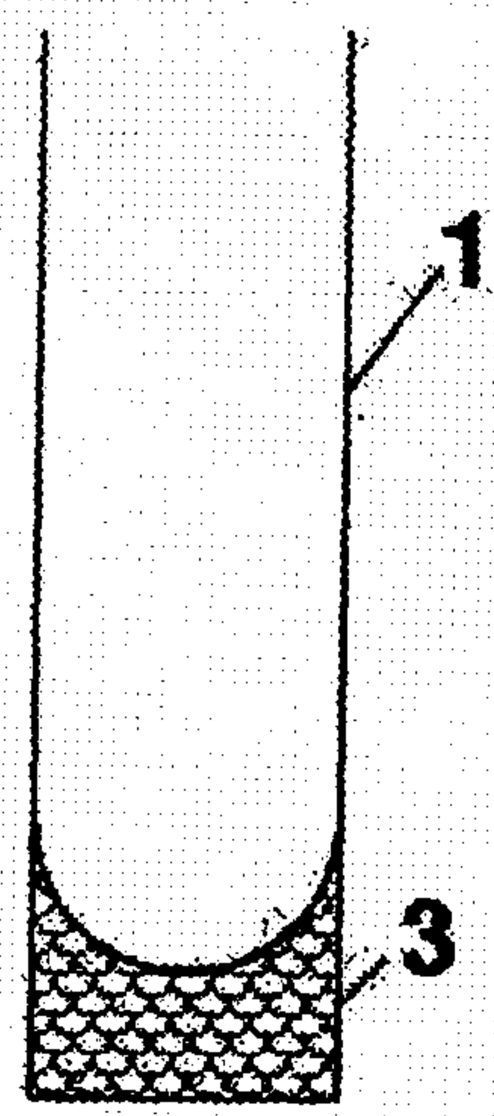
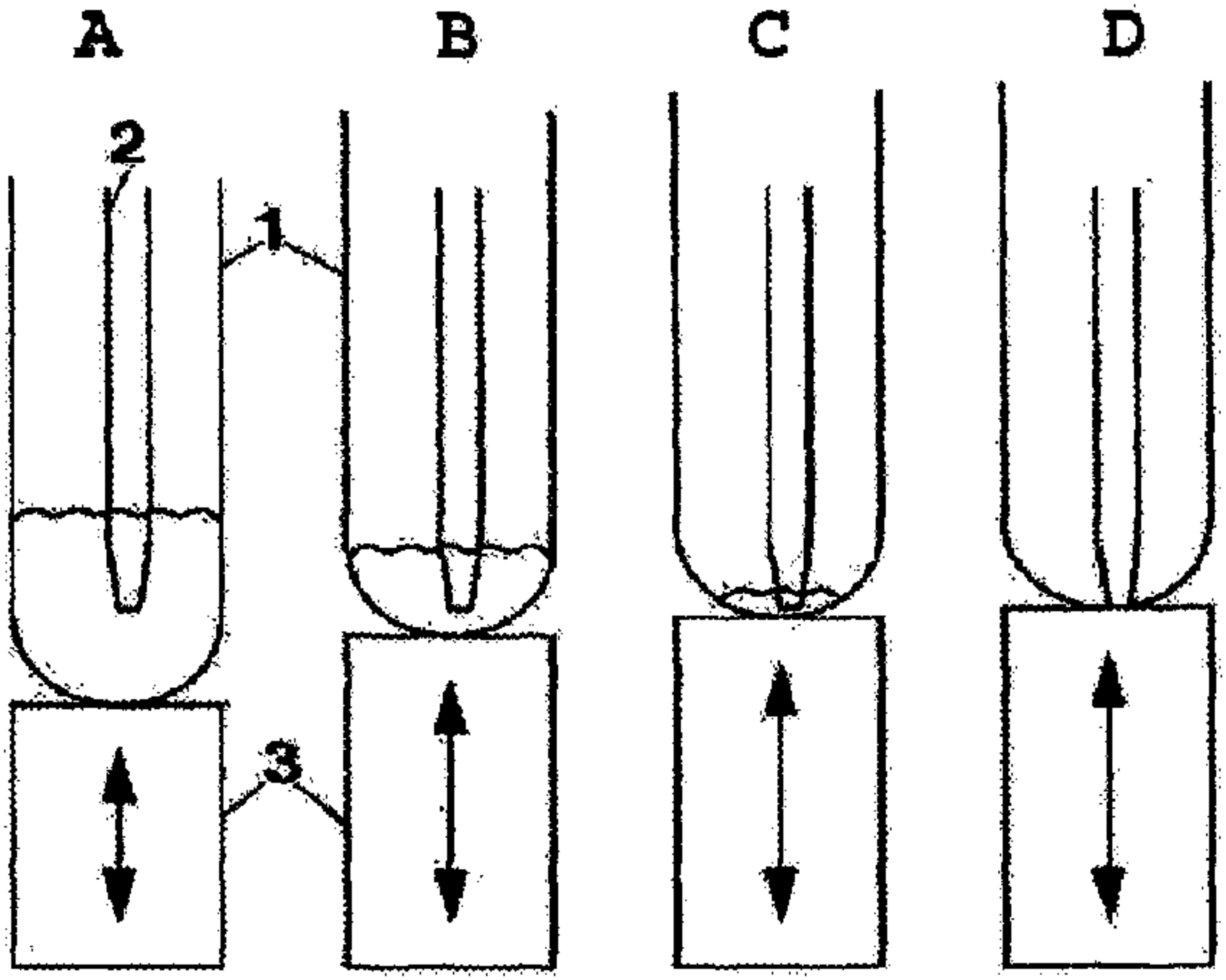


FIG. 7

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