Nov. 2, 1965 D. L. BITTNER 3,215,500

LABORATORY MIXER-SEPARATOR

Filed June 12, 1961

Fig. 1.

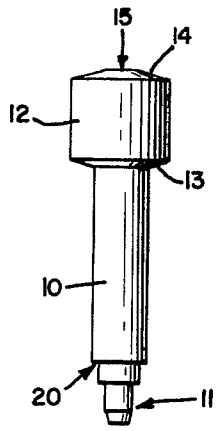


Fig. 2.

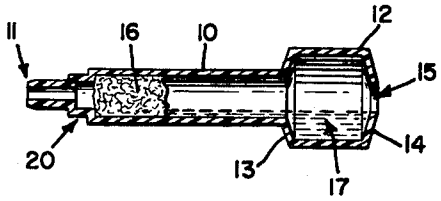
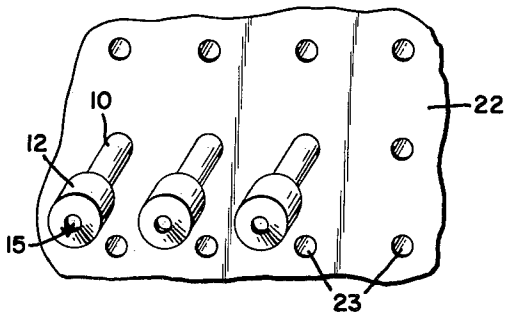


Fig. 3.



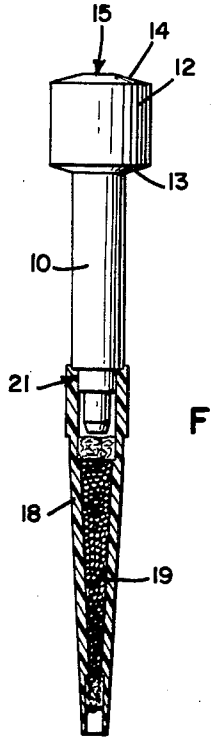


Fig. 4.

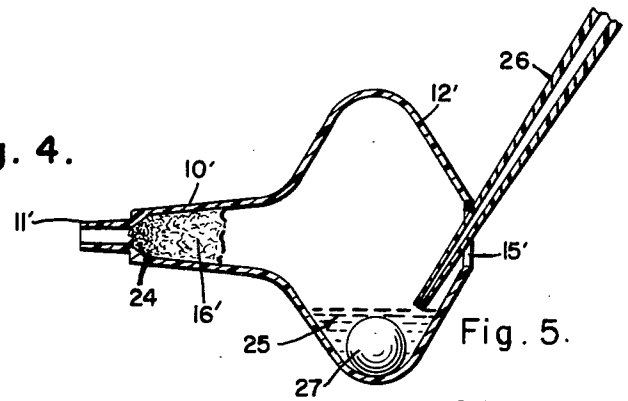


Fig. 5.

INVENTOR.
Donald L. Bittner

BY
Townsend and Townsend
attorneys

United States Patent Office 3,215,500 Patented Nov. 2, 1965

3,215,500
LABORATORY MIXER-SEPARATOR

Donald L. Bittner, 2200 Hayes St., San Francisco, Calif.

Filed June 12, 1961, Ser. No. 116,311
9 Claims. (Cl. 23—259)

This invention relates to a device and method for mixing materials, especially in micro quantities, and then directly channeling at least the liquid phase portions of the resulting mass along a contiguous restricted path where the channeled portions may, for example, be filtered.

Broadly, the present device comprises an open ended conduit having a reservoir between the ends thereof whereby materials, including at least one material in liquid phase, may be placed in the reservoir from one end of the conduit for mixing, the relation of the reservoir to the conduit being such that at least the liquid phase mixture components may then be discharged from the conduit through the other end by preselected movement thereof.

In a preferred embodiment the device provided by the present invention is a microanalytical tool for mixing reactants and then filtering the liquid phase reaction product therefrom. It comprises an open ended tube in which one end terminates in a tapered tip portion to control liquid drainage therefrom. An open ended cylinder is continuous with the other open end of the tube in end to end relation. The cylinder is axially aligned with the tube and the tube and cylinder are in fluid communication with each other at the junction of their respective abutting ends.

The other end of the cylinder which is not joined to the tube is enclosed with a cover member having an aperture therein. The aperture in the cover member is axially aligned with the tube on the other end of the cylinder. The diameter of the aperture is substantially equal to the inner diameter of the tube.

The inner diameter of the cylinder is larger than the inner diameter of the tube. As a result, when reactants are placed in the cylinder through the aperture in its cover member while the tube and cylinder are positioned in a generally horizontal attitude, the reactants will be retained for interreaction in the cylinder.

The tube optionally includes filter means. When the cylinder and the tube are positioned in a generally vertical attitude with the cylinder in a position above the tube, the liquid phase reaction product in the cylinder may be discharged down through the tube and filter means and out through the tip portion of the tube.

Reference is made to the accompanying drawing in which:

FIG. 1 shows a device provided by the present invention in side elevation wherein the device is in a vertical position.

FIG. 2 shows the device of FIG. 1 in side section wherein the device is in a horizontal position.

FIG. 3 shows the device of FIG. 1 in side elevation in combination with an ion exchange column in side section wherein the device and column are in a vertical position.

FIG. 4 shows a plurality of devices of FIG. 1 in perspective and inserted in a suitable support.

FIG. 5 shows an alternate embodiment of the device provided by the present invention in side section with the device in a horizontal position.

The principal purpose of the present invention is to provide a device and method that will make it possible to mix a plurality of ingredients in order to cause a reaction therebetween for example, and subsequently directly isolate the liquid phase resulting materials for

further manipulation without the necessity of additional handling or use of other appropriate containers or instruments.

The advantage of being able to accomplish the foregoing, particularly when dealing in micro quantities, will be best appreciated by considering a specific example. Thus, it is constantly desired to analyze blood sera for the determination of its sugar content as well as for the presence of other constituents. Usually a serum sample is available in only small quantities and therefore may be analyzed only with the application of micro techniques. Frequently the blood serum sample available does not exceed quantities as small as 50 lambda and less.

In the determination of blood sugar for example, it is first necessary to precipitate the protein in the serum so that it does not interfere and cause erroneous values in the determination of sugar. Consequently, the procedure previously following has been to precipitate the protein in one reaction vessel and then either centrifuge to remove the precipitate or pour the reaction mixture through a filter to obtain the desired liquid phase by itself.

In the case of centrifuging, only a portion of the liquid phase may be utilized, reducing the already small sample fluid even further. Moreover, centrifuging requires transfer to centrifuge cuvettes and further transfer again to a colorimeter tube or other container for use in the final analysis. The possibility of contamination and sample loss is multiplied with each additional step.

Previous filtration methods introduce similar problems. Transfer through a separate filtration instrument and then to a cuvette or other container introduces a considerable chance for contamination and sample loss. Moreover, adequate washing of the reaction vessel and then the filter is not possible since really thorough washing would result in an undesirable dilution of the sample with the large volume of wash solution required.

The present device and method overcomes all of the foregoing difficulties in that after the reactants are placed in the reaction chamber, no further transfers are necessary to obtain the sample in a condition to be analyzed. The liquid phase reaction product sample may be transferred directly to the cuvette or other device. Thus, contamination and possible sample loss are virtually a nonexistent possibility.

In addition the present device is particularly well adapted for use on a mass production basis when used in combination with a suitable support such as that shown in FIG. 3, a feature not present in prior methods and devices.

The present device in the preferred embodiment shown in FIGS. 1–4 of the drawing includes an elongated open ended tube **10**. One end of the tube terminates in a tapered tip portion **11** to control liquid drainage therefrom. The tapered tip is similar to tips found in pipettes and analogous laboratory devices well known to those skilled in the art. Since the present device is primarily designed for use in microanalysis in which quantitative results are desired, the use of a tapered tip is important to assure that the liquid passing through tube **10** is directed to the proper place without loss. Adjacent the tip end **11** of tube **10** a glass wool filter **16** is disposed.

The other end of tube **10** abuts with an open ended cylinder **12** in end to end continuous relation. Since tube **10** and cylinder **12** are open ended, fluid communication therebetween is established. Tube **10** is continuously joined to cylinder **12** by collar or shoulder member **13**. Cylinder **12** is in axial alignment with tube **10**. It should be noted that the inner diameter of cylinder **12** is larger

than the inner diameter of tube **10**. The importance of this relationship will be more fully described hereinafter.

The other open end of cylinder **12** that is not in abutment with tube **10** is enclosed with a cover plate or disc **14**. Cover plate **14** has an aperture **15** defined therein. Aperture **15** is axially aligned with tube **10** and the diameter of aperture or hole **15** is substantially equal to the inner diameter of tube **10**.

In the operation of the device, the device is held in a generally horizontal position such as that shown in FIG. 2. Reactants such as a 50 lambda sample of blood serum and a protein precipitant are placed in cylinder **12** through aperture **15** with a suitable instrument such as a pair of pipettes.

If the device is maintained in the generally horizontal position of FIG. 2, the materials placed in cylinder **12** will be contained therein in the general area marked **17**. This is because of the differential in diameter sizes of tube **10** and cylinder **12** which causes the material to lie below the possible exits consisting of aperture **15** and the inner bore of tube **10**.

Mixing is readily accomplished by rotating the device about its longitudinal axis. Such rotation does not upset the foregoing retentive capacity of cylinder **12**.

When reaction or mixing has proceeded to the desired point, the device is merely positioned in a generally vertical position such as that shown in FIG. 1. At that time the contents of chamber **12**, or at least the liquid phase contents, will flow down tube **10** by forc eof gravity through filter **16** and out tip **11**. By placing a suitable container below tip **11**, the liquid phase components from chamber **12** may be gathered directly into the container designed for the final analysis step.

Rinsing to assure quantitative recovery is readily accomplished by positioning the device in the horizontal attitude such as shown in FIG. 2, inserting a small quantity of wash diluent through aperture **15**, rotating the device about its longitudinal axis, and again reverting to the generally vertical attitude such as shown in FIG. 1.

The wash diluent is gathered in the same container in which the liquid phase materials were previously placed. One or two washings with small volumes are thereby generally adequate to assure a quantitative recovery from both the reaction chamber and the filtration area.

It will be obvious to those skilled in the art that the foregoing device is suitable for carrying out reactions in the chemical sense as well as for merely combining or mixing ingredients or even for merely washing a particular material. The term "reaction" as used throughout the specification and claims should be given a broad construction to include all of the foregoing.

Although filter **16** was referred to as a glass wool filter, any other suitable filter means may be substituted therefor such as filter papers or various types of cellulose derived filters. Any of the foregoing may be considered a mechanically acting filter since its function is merely to mechanically remove solid phase materials from liquid phase materials and to allow the passage of the liquid phase materials therethrough.

Alternatively, tube **10** may be packed with a chemically acting filter such as an ion exchange resin which will "filter" by chemically removing certain constituents of the liquid phase as well understood in the art. In addition it is suitable to combine both a chemically acting filter and a mechanically acting filter simultaneously in tube **10** to accomplish a desired result.

Yet another alternative method of chemically filtering liquid phase materials flowing through tube **10**, is to combine the foregoing described device with an ion exchange column **18** as shown in FIG. 4. Exchange column **18** is suitably filled with the ion exchange resin of the type required to accomplish the desired result.

The tip end of tube **10** is adapted to removably engage the entrance **21** to ion exchange column **18** in fluid tight relation. Thus, the tip end of tube **10** may be circumferentially notched at **20** to cooperably engage in closely nested position the entrance **21** of ion exchange column **18**.

As previously noted, the present device has a feature permitting its convenient use on a mass production basis. Thus, a vertical suport such as a board or wall **22** having a plurality of holes **23** of a diameter substantially equal to the outer diameter of tube **10** may be used to support a plurality of the devices of the present invention as shown in FIG. 3. Insertion of tube **10** in a hole **23** results in the support of the device in a generally horizontal position such as that shown in FIG. 2. In such a position the selected reactants may be placed in cylinder **12** through aperture **15**, rotated a few times to insure adequate mixing, and then allowed to remain until the reaction has gone to completion.

While the device so treated is allowed to stand, subsequent cylinders **12** may be similarly filled and treated. By the time subsequent cylinders are filled, the first filled cylinders are ready for vertical positioning for drainage into a colorimeter tube for example. An identification system such as a color code or a numbering system on the wall or support **22** and/or on the present devices may be used to avoid confusion in the recording of analytical results.

In the alternative preferred embodiment shown in FIG. 5, the device takes the form of a hollow top-like vessel. As before, the vessel includes a sphere-like reaction chamber **12'** continuous with an elongated tube portion **10'** and the internal diameter of chamber **12'** is greater than that of tube **10'**. Tube **10'** terminates in a tip **11'**.

The differences from the previous embodiment shown are in the particular shapes of the foregoing elements. Thus, tube **10'** tapers and narrows gradually in direction outwardly from chamber **12'** with the smallest internal diameter being present at the outer or tip end of tube **10'**. Adjacent to the tip end of tube **10'** the inner cross sectional area of tube **10'** tapers inwardly sharply for a relatively short distance at **24**. As a result, if a filter **16'** made from a suitable material such as Dacron or glass wool is inserted interiorly of tube **10** adjacent the tip end thereof, filter **16'** will be more tighty compressed in the sharply tapering area at **24** compared with the other parts of the filter **16'**.

This configuration results in efficient filtration since the larger solid particles in the material flowing down tube **10'** to be filtered are trapped first. The fluid readily passes down through the less compressed parts of the filter and the lower more compressed portion of the filter then serves for fine filtration. Consequently, rapid filtration through the filter **16'** is possible with the close packing of the filter necessarily impeding liquid flow only in the compressed area adjacent sharply tapering area **24** of tube **10'** after much of the filtration action has already been completed.

Continuous with tube **10'** is chamber **12'** whose cross-section radially outwardly from the longitudinal axis of the device decreases, resulting in the formation of a circumferential trough area **25**. When the device is in a horizontal position such as that shown in FIG. 5, liquid phase materials placed in chamber **12'** occupy trough **25** with its downwardly decreasing cross-section.

The foregoing configuration of chamber **12'** has the advantage, when working with very small quantities, of confining the liquid in a narrow area so that liquid will be relatively deep. This is important since when small amounts of fluid are used, the pipette employed such as pipette **26**, must be rinsed in the fluid in the reaction chamber. If the liquid in the reaction chamber is too dispersed and shallow because of the chamber configuration, it is extremely difficult to draw the fluid out with the pipette.

Preferably, the cross-section of chamber **12'** along a selected radial axis from the longitudinal axis of chamber **12'** and tube **10'** is V-shaped wherein the tip or bottom of the V may be rounded. The trough **25** is thereby formed by the sides and rounded bottom of the V.

As before, chamber **12'** has an aperture **15'** formed therein suitably axially aligned with tube **10'** through which materials to be mixed in chamber **12'** are placed. The V-shaped cross-sectional configuration along a radial axis of chamber **12'** has the further advantage of allowing the carrier for transporting the materials to be placed in trough **25** such as pipette **26** to be inserted through aperture **15** and be able to reach the lowest point in trough **25** of chamber **12'**. It is important to be able to insert the tip of a pipette to the lowest point of trough **25** when the pipette is to be rinsed with the liquid therein.

As an aid in obtaining adequate agitation and/or aeration of the materials in trough **25**, a weighted object such as a ball bearing **27** may be inserted in trough **25**. Rotation of the device along its longitudinal axis causes the ball **27** to rotate about the inner wall of chamber **12'**, causing turbulence and the desired mixing of the materials in trough **25**. Ball **27** may be an ion exchange bead if desired or made from any suitable inert material.

When the device is positioned in a generally vertical attitude to discharge the liquid phase contents therein as discussed in connection with the embodiment shown in FIGS. 1–4, ball bearing **27** falls into tube **10'** but is trapped by filter **16'** so that it does not interfere with the operation of the device.

Tip **11'** may be made to have a relatively large internal diameter so that it may be coupled with a standard injection needle such as that found in hypodermic syringes. When so coupled, the present device may be used to directly transfer the filtered liquid into a sealed vessel by inserting the needle tip through a rubber cap on the sealed vessel, for example. Tip **11'** is also suitably adapted for coupling with an ion exchange column as previously described.

The tube **10'** of the device shown in FIG. 5 tapers gradually both as to the interior thereof in contact with the filter **16'** and also with respect to the exterior surface of tube **10'**. The gradual taper of the exterior surface of tube **10'** has the advantage of permitting a tight fit when the tube **10'** is inserted in a hole such as hole **23** of support **22** as shown in FIG. 3.

The foregoing device may be made from any suitable material such as that from which laboratory equipment is generally made. Preferably the device is made from an inert plastic such as a sytrene resin. It is contemplated that the use of a suitable resin will enable the cost of the device to be low enough so that the device may be disposable after only one use. This will result in labor-saving in the cleaning of the device for reuse and avoid the possibility of contamination from inadequate cleaning before reuse.

The foregoing device may be used in the method provided by the present invention although the present method should not be construed as necessarily being limited to the use of said device. Broadly, the present method for mixing and filtering materials including at least one material in liquid phase comprises adding a plurality of said materials to a reservoir in a first position, intermixing said material while preventing discharge of any of them from the reservoir, then shifting said reservoir to a second position to cause at least the liquid phase intermixing materials to flow from said reservoir through a conduit continuous with said reservoir, and filtering said materials while flowing through said conduit.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is understood that certain changes and modifications may be practiced within the spirit of the invention as limited only by the scope of the appended claims.

What is claimed is:

1. A microanalytical tool for mixing reactants and then filtering the liquid phase reaction product therefrom comprising a tube having first and second open ends, a cylinder continuous with said first open end of said tube in end to end fluid communicating relation, a cover member having an aperture therein for the other end of said cylinder, said aperture lying generally in line with the longitudinal axis of said tube and being large enough to permit insertion of a pipette tip into said cylinder, said cylinder having a larger diameter than said tube, said diameter relationship being solely responsible for retaining selected reactants in said cylinder which have been placed therein through the aperture in its cover member for interreaction when said tube and cylinder are positioned generally horizontally, a filter in said tube, said cylinder and tube permitting discharge of substantially all of the liquid phase reaction product of the selected reactants from the cylinder down through said tube and filter when said cylinder and tube are positioned generally vertically.

2. A microanalytical tool for mixing reactants and then filtering the liquid phase reaction product therefrom comprising a tube having a first open end which terminates in a tapered tip portion to control liquid drainage therefrom and a second open end, a cylinder continuous with said second open end of said tube in end to end fluid communicating axial alignment therewith, a cover member having an aperture therein for the other end of said cylinder, said aperture being axially aligned with said tube and having a diameter substantially equal to the inner diameter of said tube, the diameter of said tube being large enough to permit insertion of a pipette tip into said cylinder, said cylinder having a larger inner diameter than the diameter of said tube, said diameter relationship being solely responsible for retaining reactants in said cylinders which have been placed therein through the aperture in its cover member for interreaction when said tube and cylinder are positioned generally horizontally, a filter in said tube, said cylinder and tube permitting discharge of substantially all of the liquid phase reaction product from the cylinder down through said tube and filter when said cylinder and tube are positioned generally vertically.

3. A microanalytical tool in accordance with claim **2** wherein said filter means is a mechanically acting filter.

4. A microanalytical tool in accordance with claim **2** wherein said filter is an ion exchange resin.

5. A microanalytical tool in accordance with claim **2** wherein said filter means includes both a mechanically acting filter and an ion exchange resin.

6. A microanalytical tool for mixing reactants and then filtering the liquid phase reaction products therefrom comprising a hollow top-like vessel having an elongated tubular portion at one end, said tubular portion being continuous with a radial reaction chamber forming the other end of the vessel, said reaction chamber having a V-shaped cross sectional area along a radial axis normal to the longitudinal axis of said tubular portion, said reaction chamber having a larger internal diameter than said tubular portion, an aperture large enough to permit insertion of a pipette tip therethrough formed in said reaction chamber axially aligned with said tubular portion whereby selected reactants may be placed through the aperture into a trough formed from the V-shaped sides of said reaction chamber and be retained therein for interreaction when said device is positioned generally horizontally, said size and shape relationships being solely responsible for retaining the reactants in said reaction chamber and a filter in said tubular portion whereby substantially all of the liquid phase reaction product in said trough may be discharged down through said tubular portion and filter when said device is positioned generally vertically.

7. A microanalytical tool in accordance with claim **6** wherein said tubular portion tapers gradually in a direction outwardly from said reaction chamber including a sharply tapered area adjacent the outward terminal end of said tubular portion whereby the filter means positioned in said tubular portion may be relatively highly

compressed in the area of said sharp taper and less highly compressed in the remaining portions thereof.

8. A microanalytical tool in accordance with claim 7 including the combination of a ball bearing in the trough formed by the V-shaped sides of said reaction chamber for promoting thorough mixing of reactants which may be placed therein when said tool is rotated about its longitudinal axis.

9. A microanalytical tool for mixing reactants and then filtering the liquid phase reaction products therefrom comprising: a hollow top-like vessel having an elongated tubular portion at one end, said tubular portion being continuous with a radial reaction chamber forming the other end of the vessel, said reaction chamber having a cross sectional area that gradually decreases outwardly along a radial axis normal to the longitudinal axis of said tubular portion, said reaction chamber having a larger internal diameter than said tubular portion, an aperture large enough to permit insertion of a pipette tip therethrough formed in said reaction chamber axially aligned with said tubular portion whereby selected reactants may be placed through the aperture into a trough formed from the sides of said reaction chamber and be retained therein for reaction when said device is held generally horizontally, said size and shape relationships being solely responsible for retaining the reactants in said reaction chamber, and a filter in said tubular portion whereby substantially all of the liquid phase reaction product in said trough may be discharged down through said tubular portion and filter when said device is positioned generally vertically.

References Cited by the Examiner

UNITED STATES PATENTS

1,547,562	7/25	Byrd	23—292
2,423,173	7/47	Brady et al.	23—292 X
2,643,940	6/53	Stevens	23—259
2,928,591	3/60	Deaver	210—496 X

OTHER REFERENCES

Thomas: "Scientific Apparatus and Reagents," Arthur H. Thomas Co., Phila., 1961, pages 772–797.

MORRIS O. WOLK, *Primary Examiner.*

GEORGE D. MITCHELL, JAMES H. TAYMAN, JR., *Examiners.*