Dec. 31, 1968 B. M. GUSTAFSON ET AL 3,419,051

DENSITY GRADIENT SYSTEM

Filed Nov. 17, 1966 Sheet 1 of 2

FIG. 1

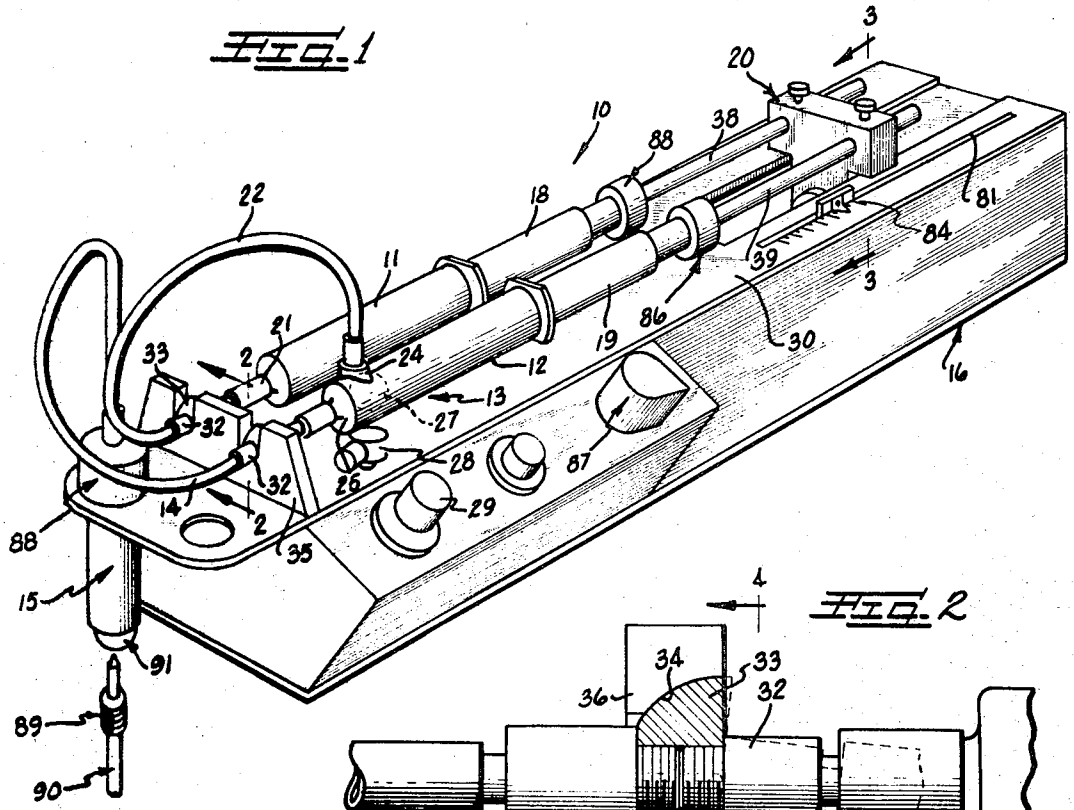
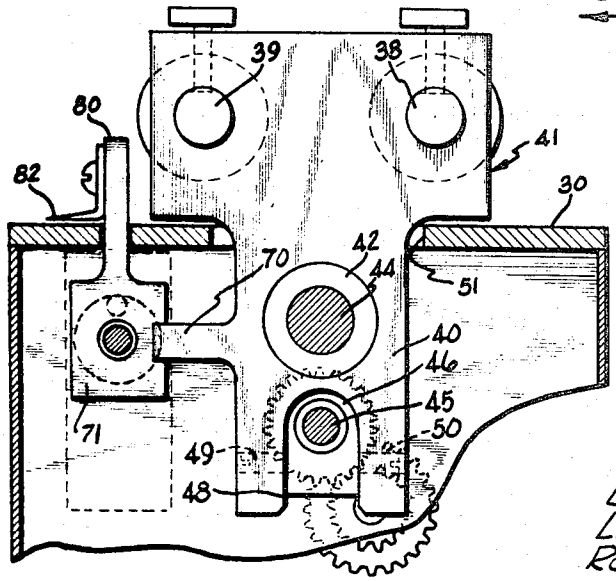


FIG. 2

FIG. 3



INVENTORS
BERT M. GUSTAFSON
LEWIS MALTER
ROBERT P. GUSTAFSON

ATTORNEYS

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Fig. 4

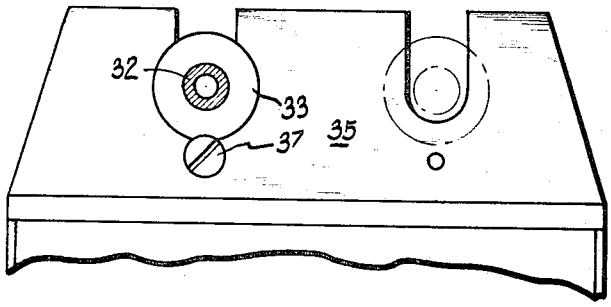


Fig. 5

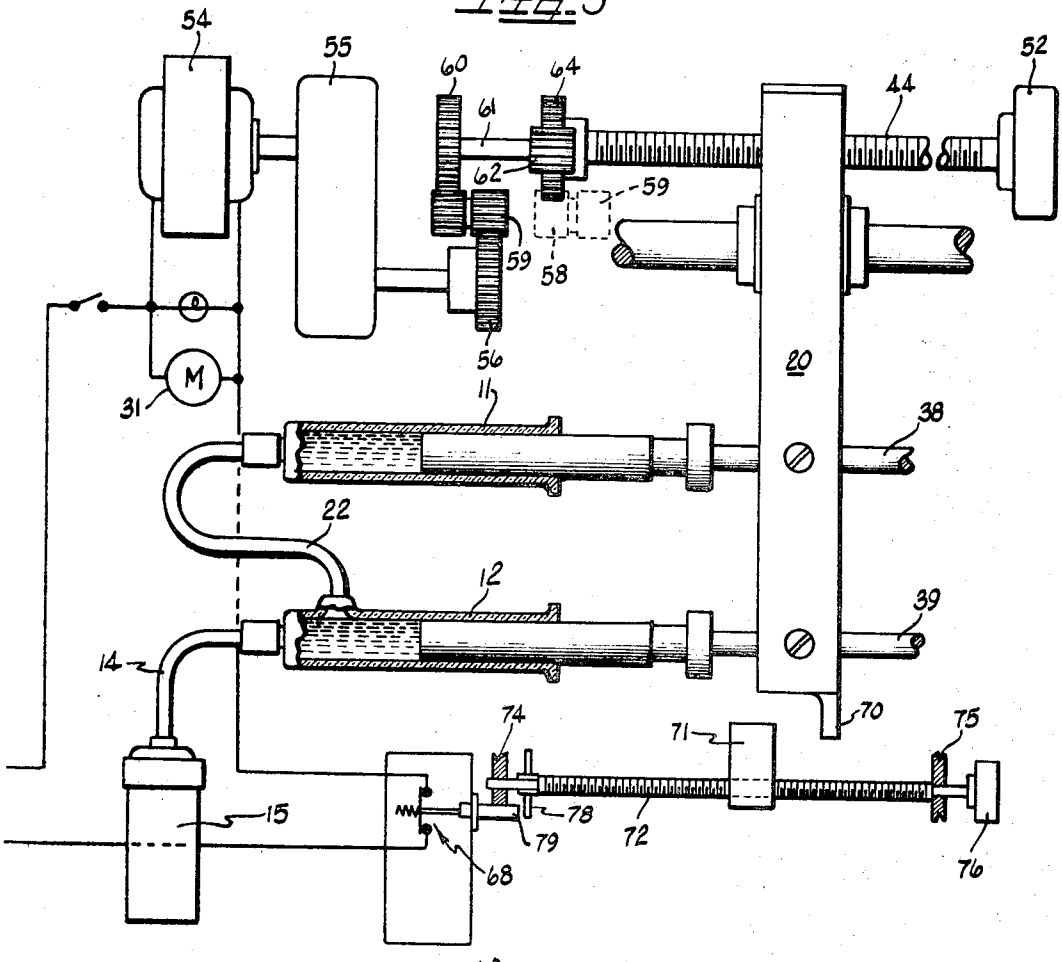
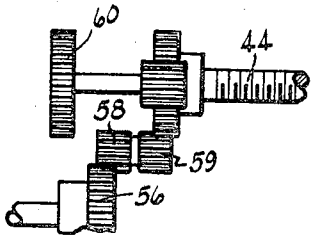


Fig. 6



INVENTORS
BERT M. GUSTAFSON
LEWIS MALTER
ROBERT P. GUSTAFSON
ATTORNEYS

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3,419,051

DENSITY GRADIENT SYSTEM

Bert M. Gustafson, 341 Princeton, Hoffman Estates, Ill. 60172; Lewis Malter, 7741 Davis, Morton Grove, Ill. 60053; and Robert P. Gustafson, 7935 W. Belmont, Elmwood Park, Ill. 60635

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9 Claims. (Cl. 141—69)

This invention relates to mixing and dispensing liquids, and more particularly to mixing and dispensing liquids of different densities, such as gradient solutions used to carry samples for analysis after sedimentation in a centrifuge.

Accordingly, the general object of the invention is to provide a machine for automatically mixing and dispensing liquids, such as gradient solutions, at a relatively high rate of production and reproducibly as compared with prior art systems.

A further object of the invention is to provide a density gradient system in which the solutions are driven from separate sources to a common mixing chamber in which the solutions are mixed after which the combined solutions are delivered to a piercing unit collector.

Another object of the invention is to facilitate the loading of density gradients into the respective chambers prior to mixing and to facilitate cleaning of the chambers after use.

Another object of the invention is to facilitate the quantitative predictable non-linear as well as linear gradient systems by interchanging various syringe pairs.

The invention also resides in a density gradient system employing two syringes driven at the same controlled rate to deliver the gradient solution from one syringe to the other syringe for mixing and then from the latter to a collecting piercing unit.

Another object of the invention is to stir the combining solutions in one syringe by a stirrer element moved by magnetic attraction to a driver on the exterior of the syringe.

Other objects and advantages of the invention will become apparent from the following detailed description taken in connection with the accompanying drawings, in which

FIGURE 1 is a perspective view of a machine for mixing and dispensing liquids such as gradient solutions and constructed in accordance with the invention.

FIGURE 2 is a sectional view taken along the line 2—2 of FIGURE 1, showing the supporting of one end of the syringes.

FIGURE 3 is a sectional view taken along the line 3—3 of FIGURE 1 showing the carriage, its drive and controls.

FIGURE 4 is a sectional view taken along the line 4—4 of FIGURE 2.

FIGURE 5 is a diagrammatic view of the apparatus constructed in accordance with FIGURE 1.

FIGURE 6 is a view of gears shifted to drive the carriage in a reverse direction.

As shown in the drawings for purposes of illustration, the invention is embodied in a machine **10** for mixing separate liquids, such as density gradient solutions of a light and heavier solution of sucrose, and for dispensing the combined liquids in the automatic and precise manner needed for density gradient solutions. The latter is the medium into which a sample of material is placed so that after a subsequent spinning of the sample and the gradient solution in a centrifuge, the sample separates and sediments at different rates in the gradient solution. After sedimentation, various layers of the gradient solution are analyzed by radiation or chromography techniques to determine the amount, if any, of the sample in the various layers.

In accordance with the present invention two different liquids, such as a light and heavy weight density solution of sucrose, are loaded into interior chambers **11** and **12** (FIG. 5) and the liquid from one chamber is continuously forced into the other chamber in which the combined fluids are mixed by a stirrer **13** and a predetermined amount of combined liquids are dispensed from the mixing chamber through an outlet **14** to a collector. Also, in accordance with the present invention, the constantly flowing, combined liquid is accurately measured and stops limit the amount of material delivered to the collector so that the combined fluids may be collected and filled for a predetermined amount without the careful attention of an operator.

In this instance, the chambers **11** and **12** for receiving the light and heavy liquids are in the form of cylinders disposed horizontally above a support frame **16** and elongated cylindrical pistons **18** and **19** are disposed partially in the cylinders and are driven at their rearward ends by a connection to a motor driven carriage **20**. Herein, the cylinders and pistons are in the form of conventional hypodermic syringes with the pistons constituting the usual plunger which is disposed in the close fitting bore of the cylinder of the syringe.

As the plunger **18** is driven by the carriage **20** further into the cylinder **11**, the light weight liquid exits the cylinder through a fitting **21** connected to one end of a conduit in the form of a tube **22** which is connected at its other end to an H fitting **24** leading to the interior of the cylinder **12**. Therefore, as the plunger **18** moves to the left (FIG. 1), the light fluid is forced from the cylinder **11** into the heavy liquid in the cylinder **12**.

For the purpose of mixing the liquids to afford a uniform mixture for the combined liquid being collected, the stirrer **13** stirs and mixes the liquids in the mixing chamber **25** which is the left end of the cylinder **12** (FIG. 1) immediately below the H fitting **24**. Herein, the liquids are stirred while the fluid is flowing and being removed continuously from the mixing chamber, and to this end a Teflon ball **27** with a metal rod therein is disposed in the mixing chamber and a magnetic driver **28** is disposed exteriorly of the cylinder and immediately beneath the mixing chamber. The driver is in the form of a T-shaped head having a pair of metal, magnetized arms of opposite polarity. The driver is journaled in an upper horizontal plate **30** of the frame for rotation about a vertical axis by a driving motor **31** (FIG. 5) secured in the frame beneath the driver. The speed and rotation of the magnetic arms of the magnetic driver is controlled by a rheostat control manipulated by a control knob **29** (FIG. 1). As the motor turns the driver, the ball moves about in the mixing chamber and during its movement mixes and stirs the two liquids of different densities prior to their leaving through the outlet tube **14**.

To support the forward ends of the cylinders **11** and **12** in a plane parallel to the top plate **30**, the forward ends of the Leur-Loks are detachably secured to a sleeve **32** (FIG. 2) on which is formed an exterior thread a semi-spherical swivel **33** (FIG. 2) for fitting in a complementary curved seat **34** in a plate **35** upstanding and extending transversely across the top plate **30** at the left end of the machine (FIG. 1). To facilitate the ready attachment and disattachment of the syringes, the seats **34** open into upwardly extending slots **36** (FIGS. 1 and 2) and a small screw **37** (FIG. 2) is threaded to engage the vertical flat rear surface on the swivel to prevent the removal of the swivel from its seat. As indicated in the dotted lines in FIG. 2 the swivel allows the cylinder body to slant or deviate slightly to maintain its alinement with the plunger as the plunger moves into the cylinder along a path advantageously alined with the axis of the cylin-

ders. Thus, the cylinders and plungers are maintained in alinement to prevent breakage of the cylinders, which are usually formed from plastic or Acrylite, while affording a quick connect and disconnect support for the syringes at their forward ends. The forward ends of the sleeves **32** are formed with a quick connect and disconnect like a Leur-Lok fitting so that the respective conduits **14** and **22** may quickly be attached or detached.

To connect the plungers **18** and **19** to the motor driven carriage **20**, the right end of each of the plungers is coupled to a drive rod **38** and **39** respectively, which are secured to the carriage **20**. The left ends of the driver rods are formed of reduced diameter (FIG. 5) and fitted in a telescoping manner in a sleeve formed at right ends of the plunger head. The drive rods extend longitudinally and horizontally from the plungers to a pair of spaced horizontal bores formed in the upper portion of the carriage **20**, and set screws threaded into the top of the carriage extend to fasten the rods to the carriage. The upper surfaces of the rods are formed with flats extending longitudinally along the rods for locking engagement with heads of the set screws (FIG. 3).

For the purpose of guiding the carriage **20** for rectangular movement longitudinally of the frame **16**, a depending leg **40** (FIG. 3) of a T-shaped carriage block **41** carries a guide bushing **42** through which extends a longitudinally extending guide rod **44** fixed in the frame. Also serving to guide the carriage for longitudinal movement is a lead screw **45** extending longitudinally beneath the slide rod and treaded in a nut **46** seated in a U-shaped opening **48** extending upwardly from the bottom of the block. Set screws **49** and **50** are threaded from opposite sides of the T-shaped block to lock and hold the nut in the U-shaped recess. The slide rod and the set screw are secured to the frame and are disposed parallel to one another with their respective axes in a common vertical plane, and thus, the carriage block is guided for rectangular linear movement with the carriage moving through the elongated opening **51** (FIG. 3) formed in the top plate **30**.

The carriage is adapted to be driven manually with turning of a control knob **52** (FIG. 5) fastened to the right end of the lead screw **44**. The carriage is, also, power driven by a motor **54** (FIG. 5) connected by suitable gearing to rotate the lead screw in either the forward or the reverse direction. As illustrated, the motor drives a gear reducer **55** which drives a shaft to which is fastened a pinion gear **56**. An axially slidable set of gears **58** and **59** are shifted between the solid line position of FIG. 5 for driving in the forward direction into the dotted line position for driving the carriage in the reverse direction. When the gears **58** and **59** are in the lefthand position (FIG. 5) the pinion is connected to a large gear **60** secured to a shaft **61** carrying a small gear **62** to drive a gear **64** which is fixed to the lead screw to turn the latter with rotation of the driving motor. When the gears **58** and **59** are shifted for reverse, as seen in FIG. 6, the gear **58** is connected directly to the gear **64** fixed to the lead screw bypassing the speed reduction gears **60** and **62** fixed on the shaft **61**.

To control the amount of liquid being dispensed by movement of the carriage, a stop is provided for the carriage **20** which when engaged by the carriage causes operation of a micro switch **66** (FIG. 5) to open the motor circuit at contacts **68** for the driving motor **54**. Herein, the depending leg **40** of the carriage block is formed with a stop finger **70** extending laterally and horizontally and movable longitudinally with the carriage to abut a stop block **71** carried on a threaded shaft **72** extending longitudinally between horizontally spaced frame walls **74** and **75** (FIG. 5). The ends of the threaded shaft are of reduced diameter and are journaled in the frame walls for turning with manual operation of a knob **76** fixed on the end of the shaft and extending exteriorly of the frame **16**. The ends of the threaded shaft also slide axially in the frame walls when the stop block is engaged by the stop finger of the carriage and shifts the threaded shaft axially to the left (FIG. 5) to move an annular disk **78** fixed to the left end of the shaft against a plunger **79** operating the contacts **68** of the micro switch. The amount of contact plunger movement is very small and the plunger is spring urged to a closed position to shift disk **78** to the right when the carriage is returned.

To determine the position of the stop block when calculating the amount of liquid to be dispensed, the stop block **71** has an upstanding indicator plate **80** guided in a narrow elongated slot **81** in the top plate **30**. The elongated slot extends approximately the full width of the threaded shaft so that the stop block can be moved to one position along the length of the threaded shaft. A pointer **82** is secured by a screw to the plate **80** to indicate the position of the stop block on a scale **84** formed on the surface of the top plate.

The preferred manner of use of the invention will be described in detail hereinafter. Initially each of the syringes is removed from the machine and is filled to a desired amount as indicated by position of the plunger end relative to the indication on the cylinder. The preferred manner of filling the cylinders is to insert a needle in the Leur-Lok fitting **21** or **25** and force the fluid into the cylinder. During filling of the cylinder **12**, a plug is inserted into the H fitting **24**. After filling the cylinders, the swivels **33** on the sleeves **32** are seated in the front plate **35** and the retaining screws **37** (FIG. 2) are fastened. Thus, the left ends of the cylinders are supported by the upstanding frame support **35**, the connection caps **85** and **86** of the plungers are then alined to receive the telescoping ends formed on the left side of the rods **38** and **39**. By loosening the set screws the rods are moved forwardly and fitted in the connecting caps **85** and **86**. The set screws are then tightened to lock the guide rods to the carriage.

The operator will then move the carriage **20** forward by twisting the handle **52** and move the stop block **71** to a position to stop the dispensing after a predetermined amount of fluid is dispensed. Since both the syringes in the preferred embodiment dispense fluid simultaneously the indicator should be positioned for one half of the amount of fluid actually desired to be dispensed.

The plug (not shown) is removed from the H fitting and the connecting flexible conduit **22** is connected between the sleeve **32** for the cylinder **11** and the H fitting **24** of the cylinder **12**. The delivery tube **14** is connected between the sleeve **32** for the cylinder **12** and the fitting on the collector **15**.

The operator will then operate the knob **29** to turn on the stirring motor **31** which rotates the magnetic driver **28** to shift the stirrer ball **27** in the mixing chamber **25** at the end of the cylinder **12**. When the stirrer driver is rotating uniformly and a good stirring action is taking place, the operator turns the control knob **87** to complete the circuit for the motor **54** which through gearing drives the lead screw **44** which in turn drives the carriage **20** to move simultaneously both plungers **18** and **19** into the respective cylinders at a uniform and controlled rate. The less dense fluid from the cylinder **11** moves through the conduit **22** into the mixing chamber **25** and is mixed by the stirrer ball with the more dense liquid and simultaneously the plunger **19** is forcing the mixed liquid outwardly through the tube **14** to the collector **15**.

When the predetermined amount of combined liquid is dispensed, the finger **70** on the carriage abuts the stop block **71** and shifts the shaft **72** to the left (FIG. 5) to actuate the micro switch contacts **68** thereby opening the circuit for the electric motor. With the motor stopped no liquid is being dispensed, and the apparatus is available for the next operation.

The syringes may be readily cleaned to remove any remaining liquid therein which, if it is a sucrose solution, will dry and coat the cylinders, plungers and tubes if the

sucrose is not removed. The plungers may be readily slid free from the cylinders and cleaned leaving the interior of the cylinders exposed for cleaning.

Another manner of using the present invention is that of forcing the sample and gradient, after sedimentation, to a suitable analyzer such as a chromography analyzer. If the sample is sedimented in a sucrose solution, each of the cylinders **11** and **12** are filled with the heavier sucrose solution. Then the motor **54** is de-energized. The sedimented sample tube is displaced in the collector **15**. Then the collector cap **88** is threaded on the collector body and conduit **14** is disengaged from connector **32** and is replaced by a conduit to the analyzer. A needle **89** formed on the end of the tube **90** is connected to connector **32**. The motor switch **87** is actuated to drive some of the solution through the outlet tube **14** and into the needle **89** to bleed the lines of air. The needle **89** is screwed into the fitting **91** formed on the bottom of the collector **15** and is screwed upwardly until it pierces the centrifuge tube and until the open end of the needle moves slightly into the solution within the centrifuge tube. With the stop block **71** set at the approximate position for the volume in the sample centrifuge tube, the motor **54** is operated to drive the carriage **20** and plungers **18** and **19** to force the solution through the conduit **14** to the bottom of the centrifuge tube. The pressure of the incoming sucrose forces the gradient solution from the centrifuge tube out through the top of the centrifuge tube in a uniform manner. When the centrifuge tube is completely filled with excess solution, the carriage will actuate the stop block **71** to open the limit switch contacts **68** and stop the motor.

From the foregoing it will be seen that with the present invention gradient solutions may be automatically mixed and dispensed in a controlled manner, or alternatively a gradient sample may be dispensed from a centrifuge tube.

What is claimed is:

1. In a mechanism for mixing and delivering liquids, comprising the combination of a support, a syringe on said support for receiving a quantity of a first liquid, a second syringe on said support for receiving a quantity of a second liquid, a movable plunger in each of said first and second syringes for forcing fluid from the syringe with linear movement of the plunger in the syringe, a carriage connected to said plungers for simultaneously moving said plungers to force fluid from said plungers, a conduit in fluid communication with said first and second syringes, a mixing chamber forming a portion of said second syringe for receiving said first liquid and said second liquid, a magnetic stirrer for stirring and mixing said liquids in said mixing chamber, a delivery conduit connected to said mixing chamber through which the mixed liquid may leave the mixing chamber, a collector for receiving the mixed liquid from the delivery conduit, and a motor to drive said carriage at a controlled rate to force the plungers to push the liquids continuously from the syringes and through the mixing chamber to the collector.

2. The combination of claim **1** including means for stopping said carriage after a predetermined amount of movement and of displacement of liquids from the syringes to the collector.

3. The combination of claim **2** in which said motor is an electric motor and in which said stopping means for the carriage includes an electrical switch for disconnecting the drive of the electric motor from the carriage.

4. The combination of claim **1** in which each of the syringes includes an outer cylinder disposed about said plunger, each of said cylinders being supported only by its plunger at one end, and a freely turnable member connected between the support and the cylinder at the other end of the cylinder, said member turning on said support to maintain alinement of the cylinder with the plunger to prevent binding of the plunger in the cylinder.

5. The combination of claim **4** wherein said carriage and said plunger are provided with telescoping members for effecting a quick connect and disconnect of the plungers to the carriage.

6. The combination of claim **1** including a manual drive means for shifting said carriage to an initial position during a setup operation prior to operation of said motor.

7. In a device for mixing and for dispensing liquids, a support, a first liquid chamber on said support for receiving a first liquid, a second liquid chamber on said support for receiving a second liquid, a mixing chamber forming a portion of said second liquid chamber for mixing said fluids, means having a passageway connecting said first chamber to said mixing chamber, means for forcing the first and second liquids to flow simultaneously and in equal proportions from the first and second chambers and through said mixing chamber at a continuous controlled rate, a stirrer in the mixing chamber for stirring the liquids together as they move through the mixing chamber, and means including an outer passage connected to said mixing chamber to afford an outlet through which said mixed liquids leave at a controlled rate.

8. In a machine for combining different densities and for dispensing the same, the combination comprising, a support, a first syringe mounted on said support for receiving a solution of a first density, a second syringe on the support for holding a quantity of a solution of a greater density, a conduit from the first syringe to deliver the lighter density solution to the second syringe adjacent a discharge end of the second syringe, stirring means including a member disposed in said second syringe adjacent its discharge end, a magnetic driver in said stirring means mounted on the support for driving by magnetic force the member inside the second syringe, a plunger in each of the respective syringes for moving longitudinally to force the solution from the first syringe through to the second syringe, means for simultaneously driving both of said plungers at a predetermined rate to force fluid from said first syringe into said second syringe and to force combined mixed solutions from said second syringe, and means for stopping the driving means after a predetermined quantity of solution is dispensed.

9. The combination of claim **8** including a stop means for stopping said driving means from forcing a quantity of liquid from said mixing chamber after a predetermined quantity of liquid is delivered.

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HOUSTON S. BELL, JR., *Primary Examiner.*

U.S. Cl. X.R.

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