United States Patent

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[54] **FLUID SEPARATORY DEVICE**
5 Claims, 4 Drawing Figs.

[52] **U.S. Cl.** **128/2**
[51] **Int. Cl.** **A61b 5/10**
[50] **Field of Search** ..... 128/2, 218 M, 218 P, 278

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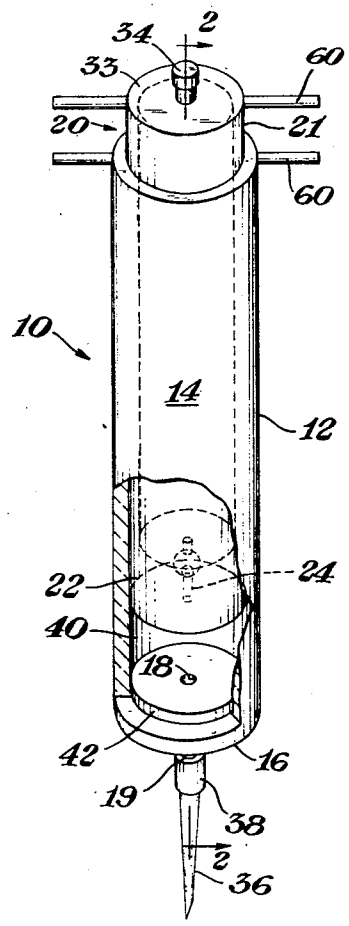
ABSTRACT: The device includes a barrel and plunger assembly for drawing the fluid into a separating chamber, chemical separating means such as an agglutinating agent for separating the phases in the chamber and means in the plunger assembly including a one-way valve for mechanical separation of the less dense supernatant phase from the more dense phase. The device is of particular utility in separation of plasma from whole blood in preparation for chemical analyses of the plasma.



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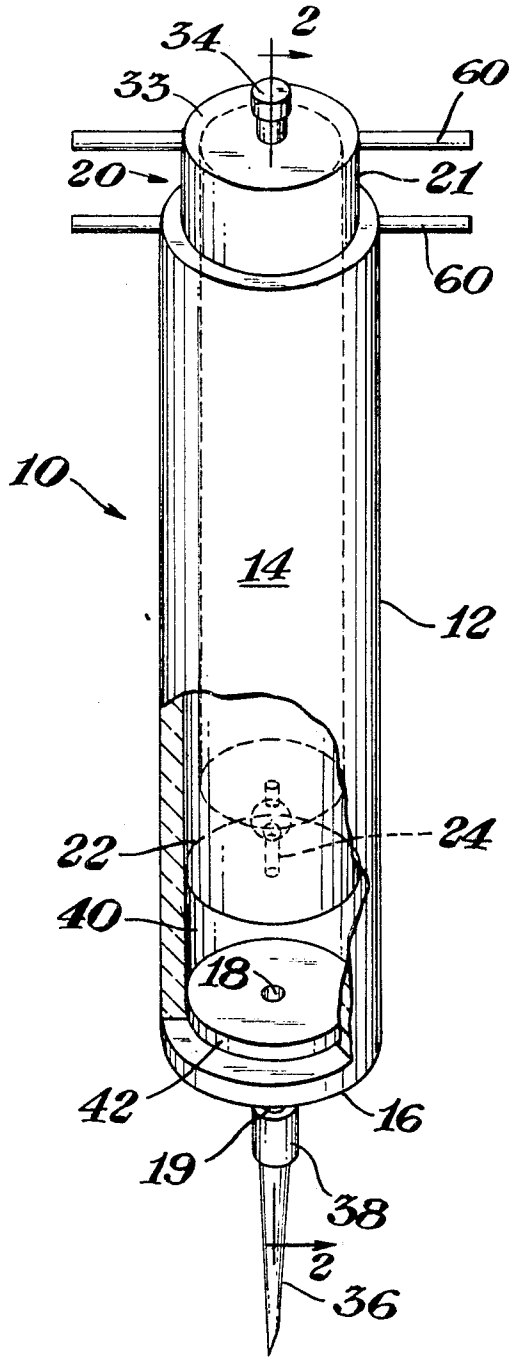

Fig. 1

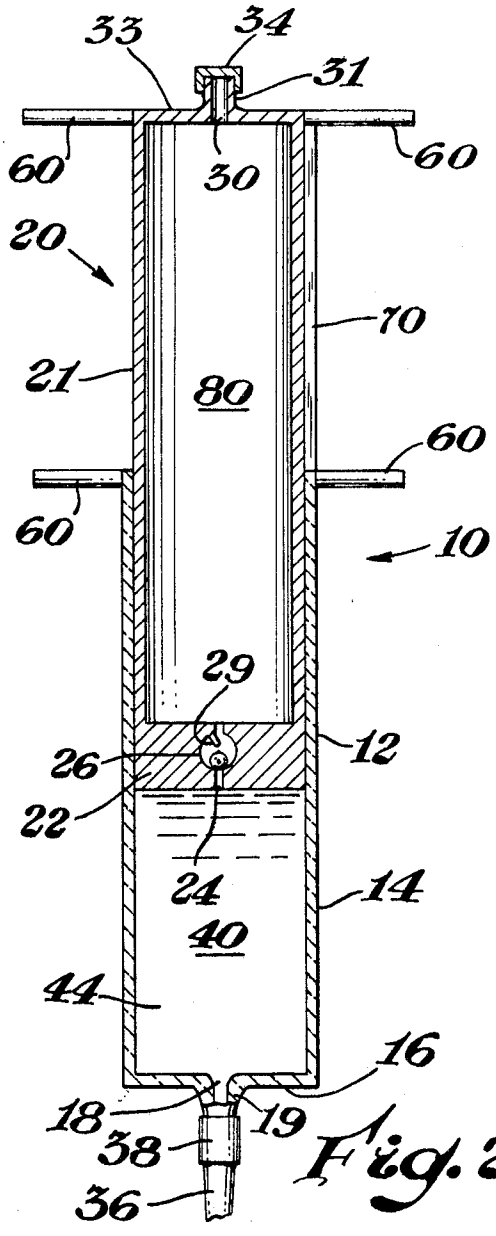

Fig. 2

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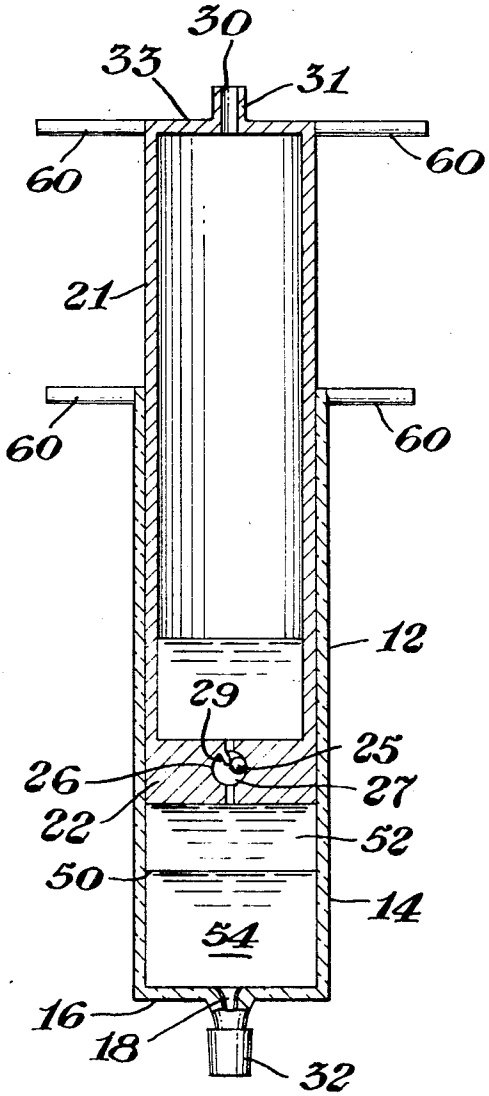

Fig. 3

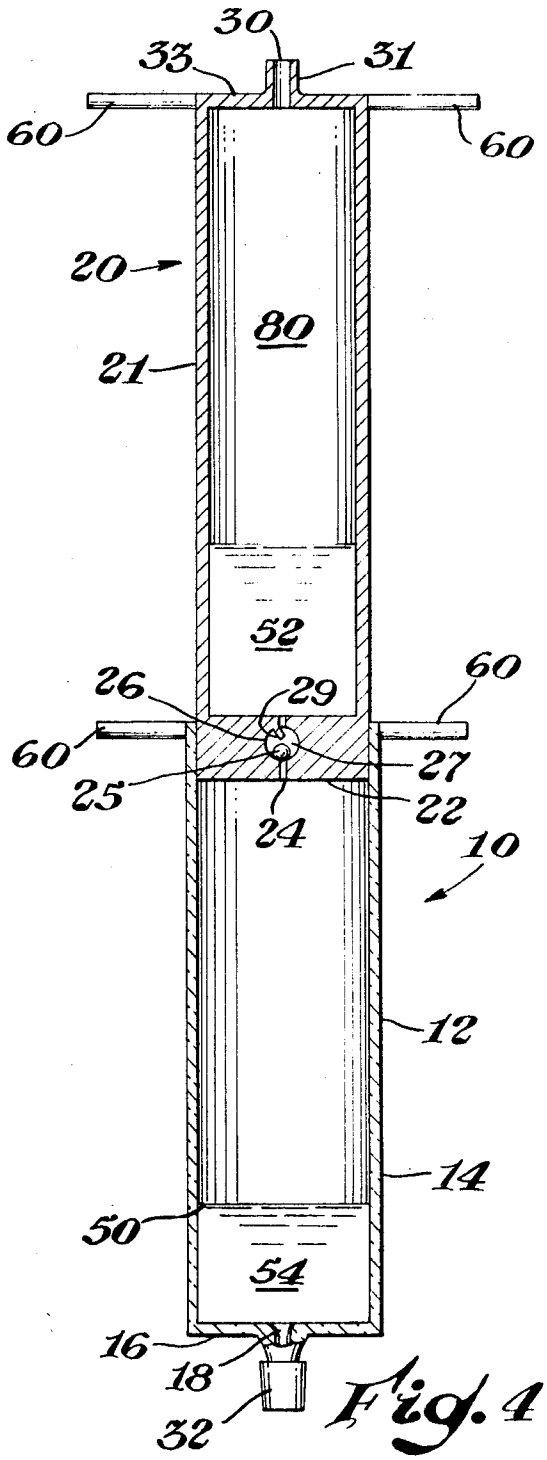

Fig. 4

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FLUID SEPARATORY DEVICE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention is directed to the separation of liquid phases from fluid mixtures. The invention is more particularly directed to separation of particular liquid phases from fluid mixtures for performing analytical chemical operations on the liquid phases, and in a preferred embodiment, for separating plasma from blood. The term "fluid mixture" herein employed to designate liquid compositions of a more or less homogeneous character but which are separable into two or more separate phases of different densities so that such separation in a gravitational field results ultimately in the disposition of the phases as layers, the more dense fluid phases being the lower layers and the less dense fluid phases forming the upper layers. The term "fluid" as employed with respect to mixtures and phases is intended to refer to solutions, liquid emulsions, colloidal dispersions, suspensions, slurries, suspensions of cells such as blood cells, tissue homogenates or bacterial cultures and the like.

2. Description of the Prior Art

The separation of particular liquid phases from fluid mixtures has been carried out by a variety of procedures, one of the most widely used procedures involving centrifugation. In the separation of plasma from blood, for example, a blood sample is drawn from a subject, mixed with an anticoagulant and placed in a centrifuge tube. The tube is placed in the centrifuge which is counterbalanced for the weight of the sample and the sample is centrifuged until the blood cells are sedimented, leaving the plasma as a supernatant fluid. The plasma can then be decanted or pipetted into a suitable container for storage, shipping or immediate clinical chemical analysis. The supernatant plasma is miscible with the more dense, cell-containing phase. The mechanical separation of the plasma requires a high degree of caution on the part of a trained analyst to avoid turbulence in the mixture resulting in resuspension of cells in the plasma. Frequently it may be undesirable to expose the fluid to the atmosphere by transferring it from initial container, to centrifuge tube, to final container as fluids such as blood can contain viruses or micro-organisms which can create a biological hazard to the analyst. Likewise, the fluid to be separated can be contaminated during the separation procedures so that certain analytical results can be affected. Moreover, the separation requires additional equipment such as the centrifuge, the additional tubes, etc. and decantation or pipetting of the supernatant fluid may require a skilled technician to prevent remixing of the separated phases during the mechanical separation thereof. Moreover, in circumstances in which control of temperature is desired during the separation, the operation is complicated by the need to either heat or cool the centrifuge, pipettes, tubes and other auxiliary equipment.

Their is a need for a single simple device for separation of fluids in which separation of fluid mixtures into phases and mechanical separation of phases can be accomplished accurately in the same device while minimizing turbulence and risks of remixing the phases.

SUMMARY OF THE INVENTION

The present invention is concerned with apparatus useful for the separation of different fluid phases from a fluid mixture. The invention is particularly directed to apparatus useful of the separation of fluid mixtures into phases of differing densities and the mechanical separation of the phases from each other.

It is an object of the invention to provide a fluid-separatory device in which collection of fluid, phase separation and mechanical separation of phases can be carried out in the same apparatus in a simple procedure involving a minimal number of distinct operations. It is a further object of the invention to provide a fluid-separatory device which is inexpensive and simple in operation and construction, and which can be employed as a container for shipping or storing the fluid phases separated therein. It is a further object of the invention to provide a device for the separation of a fluid phase such as plasma from whole blood which is adapted to permit the entire operation to be carried out in a single vessel with minimum possibility of cross-contamination between a technician using the device and the sample of blood and a minimum of cross-contamination between phases resulting from turbulence at the interface. A further object is to provide a separatory device which is adapted to operate under a variety of temperature conditions without requiring elaborate provisions for heating and cooling.

The apparatus includes a barrel having a plunger assembly movably disposed therein, so that movement of the plunger unit varies the volume of a sample chamber. The device includes inlet means for introducing a fluid mixture into the chamber and chemical means in the chamber for facilitating the separation of the mixture into a plurality of phases of differing densities. The device also includes means in the plunger unit for mechanically separating the phases by permitting one phase to flow through the plunger unit as the plunger unit is moved to the interface of the two phases and preventing such separated phase from flowing back through the plunger unit toward the interface. The inlet means of the device can be coupled to a sampling element such as a hypodermic needle so that collecting the fluid mixture, separation into phases and mechanical separation of one phase from another are accomplished in the same device. The device can also include spacer means which can be employed in lie of or in combination with the chemical means to facilitate the use of the apparatus in a centrifuge. The device is simple in construction and operation and capable of carrying out complete mechanical separation of fluid mixtures with a minimum of cross-contamination between phases or between the fluid mixture and the atmosphere. It can be employed with or without a centrifuge and is thus easily adapted to operation in a refrigerator or water bath or the like.

BRIEF DESCRIPTION OF THE DRAWINGS

Other objects and advantages of he invention will be apparent on consideration of the following description and claims and of the drawings wherein:

FIG. 1 is an isometric view of a fluid-separatory device of the invention with a portion of the barrel and plunger piston broken away to show the chemical separatory means;

FIG. 2 is a cross-sectional view of the device of FIG. 1 taken along line 2–2 of FIG. 1 and showing the device in one state of use;

FIG. 3 is a cross-sectional view of the device of FIG. 1 taken along line 2–2 and showing the device in another state of use;

FIG. 4 is a cross-sectional view of the device of FIG. 1 taken along line 2–2 and showing the device in a third state of use.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring more particularly to the drawings, the separating apparatus **10** comprises a barrel **12** having side and end walls **14, 16**; a plunger member **20**, including a plunger piston **22** slidably disposed in the barrel in fluidtight relation to the sidewall **14** thereof so that the plunger piston **22** and the walls **14, 16** of the barrel define a fluidtight separating chamber **40** of variable volume; disengageable spacer means **70** for selectively limiting movement of the plunger piston **22** in the barrel at a predetermined point whereby a predetermined minimum volume of chamber **40** is defined by the piston **22** and walls **14, 16**; closeable inlet means **18** on the barrel **12** for introducing fluid into the chamber **40**; chemical means **42** for facilitating the separation of a fluid mixture into two fluid phases, said means being disposed in the chamber **40**; means for so disposing the chemical means **42** in chamber **40**; and conduit means **24** in the plunger piston **22** for providing unidirectional fluid flow from chamber **40** through the plunger piston **22**.

The term "fluidtight" as herein employed in reference to the relationship of the plunger piston **22** and the barrel sidewall **14** means and refers to that degree of fit of the plunger piston **22** within the barrel which permits fluid to enter or leave the camber **40** only through inlet means **18** or conduit means **24**. Such fit permits fluid to be drawn into chamber **40** through the inlet means **18** against the force of gravity by the suction created by movement of the plunger piston away from the end wall **16** of the barrel **12**. The fluidtight relation of the plunger piston and the barrel thus corresponds to the relation of the piston and cylinder of a conventional lift pump or the relation of the plunger and syringe barrel of a conventional hypodermic syringe.

The barrel **12** can have any configuration or size compatible with the slidable disposition of the plunger piston **22** therein. A cylindrical configuration similar to that of a syringe barrel is preferred. The dimensions of the barrel are conveniently such as to provide a sample chamber **40** with a maximum volume of from about 5 to about 50 to 100 cubic centimeters. A barrel corresponding to the syringe barrel of a conventional 10 or 20 cubic centimeter hypodermic syringe is convenient. The barrel can likewise be of any suitable material which is sufficiently rigid and fluid resistant to contain the fluids to be separated. Glass, metal, hard rubber or synthetic plastic materials are representative materials. It is greatly preferred that the barrel **12** be transparent, so that movement of the plunger piston **22** therein and separation of fluid phases can be easily observed. COnsequently, it is greatly preferred that the barrel be constructed of a transparent material such as glass, or a transparent plastic such as polyethylene, polypropylene or polystyrene.

The closeable inlet means **18** is preferably disposed in the end wall **16** of the barrel **12** and comprises an opening or port through the end wall **16** to provide communication between the inside and outside of the barrel. In a preferred embodiment, the inlet means **18** also includes a tubular nipple **19**. The nipple **19** is adapted to be coupled to a fluid-sampling device **36** by friction fit of an adapter **38** about the nipple. Sampling device **36** can be a conventional hollow hypodermic needle. Alternately, the adapter **38** and sampling device or needle **36** can be removed and a fluidtight cap **32** can be releaseably secured over the nipple **19** by friction fit as shown in FIG. **3**, thus selectively closing the inlet means. The inlet means must be capable of closure to prevent flow of fluid from sample chamber **40** at certain times during the operation of the device, although the means by which closure is accomplished are not critical. Thus, other means may be employed to provide for selectively closing the inlet means **18**. For example, a resilient plug can be inserted into the inlet means, or the nipple can be coupled to a sampling device by means of a resilient tubular adapter which can be closed by a clamp or the like. Also, the inlet means **18** can have a one-way valve permitting fluid to enter chamber **40** through the inlet means **18**, but preventing the exit of fluid through the inlet means.

The plunger unit **20** and piston **22** can have any configuration which corresponds to the slidable fluidtight disposition of the plunger piston **22** in the barrel **12**. The plunger unit **20** can also include a plunger rod **21** which extends upwardly from the piston **22** and away from the end wall **16** of the barrel. Preferably, the plunger piston **22** and plunger rod **21** are formed as a unit from the same type of material employed in the manufacture of the barrel. The combined length of both plunger elements should be such that a portion of the plunger rod **21** extends beyond the sidewall **14** of the barrel **12** when the plunger piston **22** is disposed against the end wall **16** of the barrel. Both the barrel **12** and the plunger rod **21** can have manually graspable protrusions **60** extending outwardly therefrom to facilitate manual control of the sliding motion of the plunger piston **22** in the barrel **12**.

The apparatus **10** can also include a disengageable spacer **70** adapted to fit between a protrusion **60** on the barrel and a corresponding protrusion **60** on the plunger rod **21** as shown in FIG. **2**. The spacer **70** can be of any suitable material of sufficient rigidity to maintain the plunger rod and piston **21**, **22** in a predetermined spaced relation from the end wall **16** of barrel **12** when the apparatus is employed in a centrifuge. When **70** is engaged with protrusions **60** as shown in FIG. **2**, the downward motion of plunger piston **22** is limited so that the volume of chamber **40** cannot decrease below a predetermined limit. The dimensions of space **70** are selected so that the predetermined minimum volume of chamber **40** is at least as great as the volume of fluid mixture desired to be separated. When the apparatus and fluid mixture are centrifuged, the spacer **70** prevents the plunger piston **22** from moving under centrifugal force. A second disengageable spacer adapted to provide a second predetermined volume to chamber **40** can also be employed. Such second volume is equal to or preferably slightly greater than the volume of the more dense fluid to be retained in chamber **40** after the less dense supernatant fluid is mechanically removed. A single rectangular plate having a length and breadth corresponding to the two predetermined volumes, respectively, is conveniently employed as a spacer.

The unidirectional conduit means **24** extends through the piston **22** and includes a one-way check vale **2**. The exact type of one-way check valve to be employed is not critical and a ball valve, butterfly valve, spring-biased valve or the like can be employed. However, it is essential that the valve **26** and conduit be such as to permit fluid to flow upward through the plunger piston **22** from chamber **40** and to prevent any flow of fluid downward through the piston **22** into chamber **40**. A one-way, gravity-biased ball valve gives excellent performance in providing the required unidirectional flow, and a ball valve is the preferred one-way valve. In the valve **26**, a ball **25** is disposed in a valve chamber **27** which comprises an enlarged portion of the conduit **24**. In the upper portions of the valve chamber **27**, a stop **29** extends into chamber **27**. Stop **29** is so disposed in the upper portion of chamber **27** as to prevent the ball **25** from blocking fluid flow from chamber **27** upward, and is of such dimensions as to permit upward flow even when the ball is in its uppermost position. When the device **10** is in its normal vertical position in which the barrel end wall **16** is below the plunger piston **22**, the ball **25** is biased by gravity into a position blocking the conduit means as shown in FIGS. **1** and **2**. Suction created in chamber **40** as its volume is increased by upward sliding of the plunger piston **22** and increasing the volume of chamber **40** as shown in FIG. **2**, or the weight of any fluid disposed in the barrel **12** above the piston **22** as shown in FIG. **4** provides an additional bias toward closure of the ball valve. The upward pressure of any fluid in chamber **40** results in upward and/or lateral displacement of the ball **25**, opening valve **26** to permit fluid flow through the conduit means **24** as illustrated in FIG. **3**. Downward sliding motion of the plunger piston **22** in the barrel **12** when the input means **18** are closed increases fluid pressure in chamber **40** as the volume of chamber **40** decreases and results in opening the valve **26**. Thus, the one-way valve **26** is adapted to permit unidirectional flow from the chamber **40** through the valve when the plunger piston is moved downward or toward end wall **16**.

The device **10** preferably includes receptacle means for collecting fluid which passes from chamber **40** through the plunger piston **22**. In a preferred embodiment shown in the drawings, the plunger rod **21** extends upwardly from the plunger piston **22** and entirely surrounds the conduit means **24**, whereby the plunger piston **22** and rod **21** define a fluid receptacle or chamber **80**. Receptacle **80** is thus disposed downstream of he plunger piston **22** and conduit means **24** with respect to unidirectional flow of fluid therethrough. Receptacle or chamber **80** is closed at another end by an end wall **33** which can be a portion of the plunger rod **21**. End wall **33** includes a sealable aperture **30** surrounded by a nipple **31** extending outwardly from end wall **33**. A removable sealing cap **34** can be releasably secured over nipple **31** to seal the aperture **30** as shown in FIGS. **1** and **2**. With the cap **34** over the nipple, the pressure of air in receptacle **80** resists the flow of fluid through conduit **24** and permits the device **10** to be

handled easily without entry of fluid into receptacle **80** until such flow is desired. The cap **34** can be removed when desired to permit air enclosed in fluid receptacle **80** to escape to the atmosphere through aperture **30** as fluid passes through conduit means **24** into receptacle **80**. THus, the aperture **30** and cap **34** provide adjustable means for relief of pressure in the receptacle **80** by permitting selective venting to the atmosphere. The plunger piston **22**, plunge rod **21** and receptacle **80** included therein, and the end wall **33** are preferably formed as a single plunger unit **20** which can be separated from the barrel when a fluid phase sample has been collected in receptacle **80**. On separation of the plunger unit **20** from barrel **12** after using the device, the device serves as a pair of separate containers for separated fluids. Conventional means can be used for sealing conduit **24** after separation of the plunger unit and barrel such as a plug (not shown) adapted to fit into the conduit by friction fit, screw threads or the like, or a cap (not shown) adapted to fit over the lower end of the plunger assembly in substantially the same manner as cap **34** fits over nipple **31**.

The chemical means **42** disposed in chamber **40** can be disposed therein in any fashion which will ensure that the chemical means act on the fluid mixture to be separated and to separate the same into two phases. Thus, the chemical means can be present as a solid or a liquid in chamber **40**, for example, as a liquid film or a solid coating on the interior of the barrel sidewall **14** or on the surface of the plunger piston **22** or the barrel end wall **16**, in which case the film or coating serves as means for introducing the chemical separating means into a fluid mixture disposed in chamber **40**. The film or coating is applied to the piston or interior of the barrel by removing the plunger unit from the barrel, applying the chemical means and replacing the plunger unit in the barrel. Alternately, it can be present as a mixture with the fluid to be separated, having been mixed with such fluid either prior to or subsequent to the placing of the fluid in the device **10**, in which case the inlet **18** serves as means for introducing the chemical separating means into chamber **40** and thus into contact with the fluid mixture. It is greatly preferred, however, that the chemical means be disposed in chamber **40**, whether or not a fluid to be separated is simultaneously present.

The chemical means can be any agent suitable for enhancing separation of the particular liquid mixture into two separate phases. When the liquid is an aqueous emulsion such as emulsions of various organic liquids and water, or of fats or oils and water, the chemical means can be an emulsion-breaking agent. When it is desired to separate colloidal dispositions or protein suspensions or solutions into supernatant liquid and a liquid phase containing solid material, a flocculant or a protein precipitant can be employed. When the liquid mixture is a suspension of cells such as blood, aqueous bacterial cultures or tissue homogenates, the chemical agent can be agglutinant, that is, an agent which enhances the agglutination or clumping together of cellular material. In particular applications, selective chemical separating agents capable of separating particular liquid mixtures into particular fluid phases can be employed; for example, when the liquid mixture is milk, an emulsion-breaking agent such as amyl alcohol can be employed to separate the fat from the heavier, aqueous colloidal phase or a protein precipitant such as silver nitrate or lead acetate can be employed to separate the milk into a protein-free liquid phase and a liquid phase containing precipitated flocculated protein. The chemical separating means cooperates with the other elements of the device to facilitate the complete separation of the desired fluid phase and, in many cases, the chemical separating means determines the nature of the supernatant fluid separated from the fluid mixture. The exact chemical separating means to be employed is dependent upon the particular fluid mixture to be separated by the use of the device and the particular liquid phases to be obtained, it being essential only that the chemical means facilitate the separation of the liquid mixture into two or more separate liquid phases of different specific gravities.

Various chemical separating agents which can be employed in the separation of particular fluid mixtures are disclosed by Clayton, Theory of Emulsions,5th Edition, chapter XIII, Blakiston Company, New York (1954) and by Becher, Emulsions: Theory and Practice, Second Edition, chapters 5 and 9, Reinhold, New York (1965). Agents useful in precipitation of colloidal materials or suspensions are disclosed by Shaw, Introduction to Colloid and Surface Chemistry, chapters 8 and 10, Butterworths, London (1966). Chemical means useful in the separation of biological fluid phases in fluid mixtures such as blood are disclosed by Henry, Clinical Chemistry: Principles and Techniques, Hoeber Division of Harper and Rowe (Second Printing, 1964).

The device of the invention has particular utility in the separation of plasma or serum from whole blood, typically in preparation for chemical analysis of various plasma or serum components. In such use, the chemical separating means **42** comprises an agglutinant and, optionally, an anticoagulant, and preferably both an agglutinant and an anticoagulant. The agglutinant serves to bring about the clamping together and precipitation of the blood cells and to separate the blood into a cell-free liquid phase and a more dense liquid phase containing the precipitated clumps of cells. Representative agglutinants which can be employed as chemical separating means include fibrinogen, polyvinylpyrrolidone, hemagglutinin, phytohemagglutinin and dextran. The preferred agglutinant is fibrinogen. When an agglutinant is the sole chemical-separating means, clotting of blood takes place as well as agglutination. In such a case, serum is obtained as the less dense liquid phase above the precipitated cells. Separation of serum rather than plasma is desirable in certain situations. In other cases, plasma is desired, and the loss of plasma components such as prothrombin which are involved in clot formation is undesirable. Thus, in order to separate plasma from blood in the device of the invention, the chemical agent must comprise an anticoagulant, that is, a chemical agent which inhibits the clotting of blood, as well as the agglutinant required to separate the blood cells into a separate liquid phase. Representative anticoagulants which can be employed include heparin and synthetic heparinlike compounds; bishydroxycoumarin; oxalate anticoagulants such as potassium oxalate or ammonium oxalate; citrate anticoagulants such as trisodium citrate, tripotassium citrate and mixtures of trisodium citrate, citric acid and dextrose; alkali metal salts of ethylenediaminetetraacetic acid; potassium fluoride and the like. Heparin is the preferred anticoagulant.

Either the anticoagulant or the agglutinant or both can be disposed in the chamber **40** prior to the introduction of blood thereinto. Preferably, both the anticoagulant and the agglutinant are disposed as a solid layer or deposit on an internal wall of barrel **12** or the plunger piston **22**, and disposition of a solid mixture of the two agents on the surface of end wall **16** is preferred. The chemical means **42** for separation of plasma from blood is conveniently disposed in chamber **40** by withdrawing the plunger unit **20** from the barrel, pouring a solution of heparin and fibrinogen into the barrel and allowing the solvent to evaporate, leaving the mixture of anticoagulant and agglutinant as a solid layer on end wall **16**.

THe amount of chemical separating means to be employed depends in part on the amount of fluid mixture to be separated and on the result to be achieved. THe chemical separating agent should be employed in an amount such that the dilution and admixture of the agent with the particular fluid mixture provides an effective concentration of the agent in the mixture. An effective concentration is sufficient to produce the desired effect, emulsion breaking, precipitation, clot inhibition, agglutination or the like. In plasma separation for example, the chemical means **42** includes sufficient heparin to provide an anticoagulant concentration of from about 10 to about 20 to about 50 milligrams of heparin per 100 milliliters of blood, and sufficient fibrinogen to provide an agglutinating amount of from about 50 to about 200 to about 600 milligrams of fibrinogen per 100 milliliters of blood.

In the operation of the device **10**, a fluid mixture **44** to be separated is drawn into chamber **40** through the inlet means **18** as the plunger piston **22** is slidably moved away from barrel end wall **16**. Inlet means **18** is then closed by cap **32** and the fluid mixture **44** is mixed with the chemical-separating means **42** which has been disposed in chamber **40** prior to introduction of fluid mixture **44**. The device **10** is then maintained in a substantially vertical position as shown in FIG. **2** until the fluid mixture **44** separates into a less dense supernatant fluid phase **52**, situated in the upper portion, and a more dense fluid phase **54**, situated in the lower portion of chamber **40**. Alternately, a spacer **70** is engaged between protrusions **60** on the barrel **12** and plunger rod **21** to maintain the minimum volume of chamber **40** at least equal to the volume of fluid mixture **44**, and the device **10** is centrifuged by conventional procedures to dispose the more dense phase **54** in that portion of chamber **40** nearest end wall **16**. Depending upon the fluid mixture employed and the type of separation desired, the liquid phases can be separated by centrifugation while the spacer is engaged without employing a chemical-separating means. The cap **34** is then removed from aperture **30** and when a spacer **70** has been employed, the spacer is disengaged or removed. The plunger piston **22** is then slidably moved downward toward barrel end wall **16**. As plunger piston **22** moves into the chamber **40**, the upper less dense fluid phase **52** passes through unidirectional conduit **24** and valve **26** into the fluid receptacle **80** as shown in FIG. **3**. Downward motion of the plunger piston **22** is continued until the plunger piston **22** reaches the interface **50** between the two liquid phases. Alternately, a second spacer is engaged with a protrusion **60**, the second spacer being adapted to prevent downward motion of the plunger piston beyond the interface **50**, and the plunger piston **22** is moved downward until further downward motion is prevented by the spacer. Since the less dense liquid in receptacle **80** is prevented from returning to chamber **40** by one-way valve **26**, mechanical separation of the two liquid phases **52**, **54** is complete at this stage an the plunger unit **20** can be moved upward as shown in FIG. **4**. If desired, cap **32** can be removed from the barrel nipple **19** and the more dense fluid **54** can be drained from chamber **40** through the inlet means **18**. Also, the plunger unit **20**, including the less dense liquid phase **52** disposed in receptacle **80**, can be removed and aperture **30** can be capped and conduit **24** closed in any convenient manner to provide a closed receptacle for storing or handling the fluid phase **52**. Since the device can be employed without centrifugation, the temperature at which separation is carried out can be controlled easily by placing the device in a refrigerator, incubator, ice bath, water bath or the like.

In the separation of plasma from whole blood, the chemical means **42** employed is preferably a solid film of heparin and fibrinogen, and the mixture of the anticoagulant and the agglutinant is disposed as a film on end wall **16** as shown in FIG. **1**. The chemical means is deposited on the end wall as described above, prior to using the device. The device equipped with a needle **36** and adapter **38** on inlet means **18** and a cap **34** on aperture **30** is employed to draw a sample of blood from a subject into chamber **40**. The device **10** is inverted, the needle and adapter **36**, **38** are removed and cap **34** is placed on inlet means **18**. With the inlet means thus closed, the anticoagulant and agglutinant are mixed with the blood fluid mixture **44** by inverting the apparatus several times. The device is then placed in an upright position as shown in FIGS. **2**—**4** and held for a short period while the plasma separates from the blood cells as an upper fluid phase **52**. Generally, the separation is sufficiently rapid so that plasma occupies the upper 45 to 55 percent of the sample chamber volume after about 30 minutes or the upper 50 to 60 percent about 1 hour. When it is desired to separate serum or plasma from whole blood by employing the device in conjunction with a centrifuge, a spacer **70** is employed as described above. When a centrifuge and spacer are employed in separating plasma, the chemical separating means can comprise an anticoagulant alone. With serum, rather than plasma, is separated in this procedure, the chemical means can be omitted or can comprise an agglutinant alone. After the phases have separated to the desired extent, cap **34** is then removed from aperture **30** and the spacer **70**, if used, is disengaged. The plunger piston **22** is then urged downward toward the interface **50** of the plasma phase and the blood cell phase. The plasma flows through the conduit means **24** into receptacle **80** as shown in FIG. **3**. If desired, the plunger piston can be moved slowly downward during the holding period to provide for gradual continuous flow of plasma through conduit **24** to receptacle **80** as the separation of phases by agglutination of the cells progresses. When the plunger piston **22** reaches the interface **50** or a point slightly above it, the plunger unit **20** is withdrawn upwardly from the barrel **12** as shown in FIG. **4**. Cap **34** is replaced on nipple **31** and, if desired, conduit means **24** can be sealed by a plug or the like. The plasma separated in the device can be shipped or stored in the receptacle **80** and is suitable for analytical clinical chemical purposes.

It will thus be seen that the device can be described as an improved syringe similar to conventional hypodermic syringes. Thus, the device **10** has a barrel **12** equipped with a detachable needle **36** and a plunger unit **20** including a plunger piston **22** and plunger rod **21**. In the device of the invention, however, the plunger piston includes conduit means **24** for providing unidirectional flow from the barrel into a receptacle **80** enclosed within the rod **21** and means for selectively preventing loss of fluid from the barrel **12** such as the cap **34** over inlet means **18**. Moreover, the device **10** includes chemical separation means **42** in chamber **40** of the barrel **12** and means such as inlet **18** or the removable plunger unit for disposing chemical means **42** in chamber **40**. Thus, the device corresponds to a syringe which is adapted to bring about the separation of fluid mixtures disposed therein by chemically enhanced separation of the fluid mixture into phases and also by mechanical separation of one liquid phase from another.

The device can be modified, for example, by the choice of particular unidirectional flow means in the plunger piston, the choice of particular closeable inlet means on the barrel or means of closing the aperture on the receptacle in the plunger unit. Modification of the chemical-separating means by the choice of particular means to accomplish particular functions in the separation of particular fluid mixtures can be carried out to adapt the device for use in a variety of separatory applications. Also, it will be apparent that in some applications, one or more spacers can be employed to permit centrifugation of the device and omission or variation of the chemical separating means. Mechanical means for moving the plunger piston can also be employed, with such means being controlled by timers or sensing means such as photoelectric devices for actuating the mechanical means when a predetermined amount of supernatant fluid has separated from the fluid mixture.

What I claim is:

1. A method for separating a fluid mixture into a plurality of fluid phases of differing densities within a syringe having a barrel, including a sidewall and an end wall, inlet means in a wall of the barrel for admitting a fluid mixture thereto; a plunger slidably disposed in the barrel in fluidtight relation to the sidewall thereof so as to form a chamber of variable volume in the barrel, means for selectively closing the inlet means; conduit means on the plunger for providing unidirectional fluid flow through the plunger from the chamber; and a receptacle on the plunger surrounding the conduit means and downstream thereof, the method comprising:

a. drawing a fluid mixture to be separated through the inlet means and into the chamber,

b. mixing the fluid mixture in the chamber with a chemical means for facilitating the separation of a fluid mixture into a plurality of fluid phases of differing densities,

c. closing the inlet means, and thereafter

d. holding the syringe in a vertical position with the plunger above the defined chamber until the fluid mixture separates into a plurality of phases of differing densities,

e. moving the plunger downward into the chamber toward the interface resulting from separation of the mixture and simultaneously venting the receptacle to atmosphere, whereby the uppermost liquid phase flows through the conduit means into the receptacle;

f. terminating the downward motion at a point in said chamber not below the interface;

g. and thereafter withdrawing the plunger, receptacle and the liquid phase therein from the barrel.

2. The method of claim 1 further comprising the step of sealing the receptacle from communication with atmosphere during the mixing and holding steps.

3. THe method of claim 1 wherein the chemical means for facilitating separation comprises an agglutinant.

4. THe method of claim 3 wherein the chemical means for facilitating separation further comprises an anticoagulant.

5. THe method of claim 4 wherein the anticoagulant is heparin and the agglutinant is fibrinogen.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,596,652 **Dated** 3 August 1971

Inventor(s) James W. Winkelman

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In column 2, line 32, change "lie" to -- lieu --.

Column 5, line 26, delete "liquid in" and insert -- liquid disposed in --; in line 48, delete "dispositions" and insert -- dispersions --.

Column 6, line 21, delete "clamping" and insert -- clumping --.

Signed and sealed this 11th day of April 1972.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

ROBERT GOTTSCHALK
Commissioner of Patents