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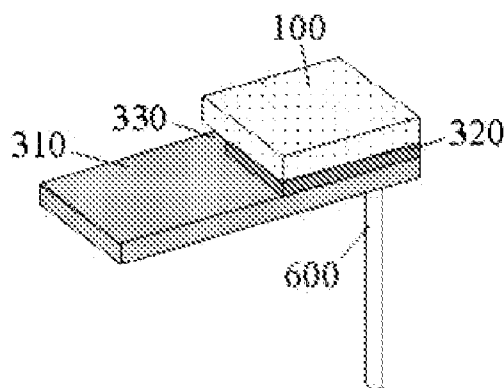


FIG. 2a

(57) Abstract: A new method is disclosed for extracting plasma from whole blood and metering the amount of plasma to an exact volume for dispensing into a diagnostic test, in a fully automatic and self-contained device. The device can be used in resource limited settings by unskilled users to facilitate sophisticated medical diagnostic testing outside of a hospital, clinic or laboratory.



AUTOMATIC PLASMA SEPARATION AND METERING

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. application number 62 / 195,281, filed 21 July 2015 and U.S. application number 62 / 249,922, filed 02 November 2015, which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0001] Field of the Invention: This invention discloses a method of extracting plasma from whole blood in an automatic fashion using a plasma separation membrane, capillary forces, and a novel capillary reset valve or mechanism (CPR-Valve). The CPR-Valve automatically overcomes the breakthrough pressure of the plasma separation membrane allowing the plasma extraction, collection and metering processes all to take place without any external forces, energy or action on the part of the user or need of additional support equipment.

[0002] Description of Related Art: Many attempts have been made at separating plasma from whole blood in a stand-alone device, as a means of replacing the common method of centrifugation. Plasma is often required for the detection of blood-based biomarkers because, in many cases, the cellular components of blood interfere with detection of these biomarkers. Centrifugation, however, is a fairly complex task involving skilled personnel, complex, heavy and large equipment, and electrical power. In addition, a means for obtaining the whole blood is needed, which is usually performed by a venous puncture and blood draw by another skilled person, namely a phlebotomist. Finally, another or one of the same skilled workers is needed for performing the centrifugation, measuring the required volume of plasma, and dispensing the plasma into the diagnostic device, usually using a pipette. In automated systems some of these manual steps can be replaced with robotic processes of loading, spinning, measuring and dispensing. However, these automated systems are usually even more complex, expensive, large and sophisticated than a simple centrifuge. The need for replacing all of these steps in a simple, affordable, and easy to use device is the focus of numerous, as yet commercially unsuccessful, efforts.

[0003] Many attempts at replacing the centrifuge use commercially available Plasma Separation Membranes (PSM), such as the Pall Vivid™ PSM or International Point of Care Primecare PSM. Numerous scientific articles have been published describing devices comprised of these membranes, as well as support structures required for adding the whole

blood, collecting the separated plasma and, in all cases, some means of overcoming the breakthrough pressure of the PSM to allow the plasma to pass through the membrane and be collected.

[0004] Many of these articles detail the biochemical nature of the plasma that is collected and compare it to plasma derived from centrifugation. Most comparisons are favorable, which should lead to rapid adoption of these processes due to the commercial need of such technology. However, it has not, and there is, to date, no readily available and commonly used centrifuge replacement device. This is most likely due to the complex method of sample handling, collection, difficult, complex, or expensive method of overcoming the breakthrough pressure of the PSM, and related issues that lead to designs that are not commercially viable, either due to cost, complexity of use, or poor performance.

BRIEF SUMMARY OF THE INVENTION

[0005] The disclosed technology details a new method of overcoming the breakthrough pressure of hydrophilic membranes, in this case the Plasma Separation Membrane (PSM), and the design advantages made possible by this new method. These design advantages include the ability to design exactly where the plasma breaks through, how the flow of plasma through the membrane proceeds, where it stops, and how all parameters can be easily controlled using passive capillary forces, leading to a completely automatic, self-contained, disposable device that is easily used and inexpensive to manufacture.

[0006] A device for overcoming the breakthrough pressure of the PSM makes use of a new mechanism described as a Capillary Pressure Reset (CPR) Valve or mechanism. This valve is comprised of a soluble matrix that has a high enough capillarity to draw liquid through a hydrophilic membrane or filter (e.g. the PSM) under passive capillary forces, thereby eliminating the membrane's inherent breakthrough pressure, and then dissolving in the extracted liquid (the plasma) and releasing the liquid into a new geometry that has lower capillarity.

[0007] By placing the soluble matrix comprising the CPR-Valve in a strategic location at one end of a plasma pooling or collection channel, the initial breakthrough point and direction of flow of the plasma can be design to proceed in a repeatable manner. This flow or filling process can be designed to ensure no bubbles are trapped, which can lead to accurate, repeatable filling of a precise geometry of known volume, leading to the plasma being metered to a known volume prior to dispensing.

[0008] Several examples of how the technology is used, and specific details of the design parameters of complete systems, are disclosed.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

[0009] The following drawings illustrate exemplary embodiments for carrying out the invention. There are, in fact, many possible configurations, housings, flow systems, entrance and exit point designs, flow patterns, Capillary Pressure Reset(CPR)-Valve placements, dimensions and geometries including rectangular or cylindrical flow channels, and liquid flow driving forces possible in various embodiments of the invention. The following examples only serve to illustrate principles discussed in this disclosure, and are not meant to be limiting in any way in converting the principles discussed in this disclosure into physical form, and are not necessarily to scale as may be used in a physical system. Like reference numerals refer to like parts in different views or embodiments of the present invention in the drawings.

[0010] *FIG. 1* illustrates the basic concept of CPR-Valve placement in contact with the bottom surface of a Plasma Separation Membrane (PSM), and the flow of plasma to fill a space under the PSM.

[0011] *FIG. 2a* and *b* illustrates assembled (a) and exploded (b) views of a structure useful for separating plasma from a whole blood sample and delivering a metered volume of that plasma into a capillary tube inserted into the plasma pooling area according to an embodiment of the invention.

[0012] *FIG. 3* illustrates a layer by layer view of a thermoformed or injection-molded structure useful for separating plasma from a whole blood sample introduced into a metering input capillary and the plasma collected into a specially modified capillary tube designed to also function as a removable pipetting device according to an embodiment of the invention.

[0013] *FIG. 4* illustrates a similar design as *FIG. 3*, except that this design is comprised of laminated layers rather than injection molded or thermoformed parts according to an embodiment of the invention.

[0014] *FIG. 5* illustrates another laminated plasma extraction and metering device where the metered plasma is dispensed directly from the body of the device, rather than collected into a removable capillary pipette according to an embodiment of the invention.

[0015] *FIG. 6* illustrates an alternative geometry of a plasma extraction and metering device where the separated plasma is collected into two removable capillary pipettes useful

for aliquoting the whole blood input into two separate plasma outputs for dispensing into two different diagnostic assays according to an embodiment of the invention.

[0016] *FIG. 7* illustrates a multi-layered laminate design with a short and deep plasma collection channel and no vent. In this design metering is entirely controlled by the output capillary pipette according to an embodiment of the invention.

[0017] *FIG. 8* illustrates a design where the CPR-Valve serves a dual purpose, namely to draw plasma through the PSM and to overcome the capillary stop junction at the entrance of the large inner-diameter capillary pipette by drawing plasma into the capillary pipette, according to an embodiment of the invention.

[0018] *FIG. 9* illustrates further a profile view of the CPR-Valve and its placement between the PSM and output capillary pipette in order to perform the dual purpose mentioned in the previous paragraph describing *FIG. 8*, according to an embodiment of the invention.

[0019] *FIG. 10* illustrates a profile view of the CPR-Valve and its placement between the PSM and a reagent pellet or disk and the output capillary pipette according to an embodiment of the invention.

[0020] *FIG. 11* illustrates a profile view of a multi-layered laminate design showing an extension of the plasma pooling area useful for improving the efficiency of a device according to an embodiment of the invention.

[0021] *FIG. 12 a* and *b* illustrate the use of a capillary stop junction near the outlet of the input capillary to ensure precise volume control of the input whole blood added to the PSM according to an embodiment of the invention.

DETAILED DESCRIPTION OF THE INVENTION

[0022] Certain embodiments as disclosed herein provide for an automatic plasma separation device. After reading this description it will become apparent to one skilled in the art how to implement the invention in various alternative embodiments and alternative applications.

Although various embodiments of the present invention will be described herein, it is understood that these embodiments are presented by way of example only, and not limitation. As such, this detailed description of various alternative embodiments should not be construed to limit the scope or breadth of the present invention.

[0023] Capillary Pressure Reset (CPR)-Valve: The breakthrough pressure of a membrane is defined as the pressure required to force liquid (filtrate) through the downstream surface of a

membrane. In simplified form the breakthrough pressure can be considered as multiple capillary stop-junctions as the pores on the bottom surface of the membrane open to the space below the membrane. The breakthrough pressure is dependent on the membrane material composition, pore size and liquid filtrate properties. In the disclosed design the soluble matrix of which the CPR-Valve is comprised is in physical contact with the bottom surface of the Plasma Separation Membrane (PSM) and represents a zone of higher capillarity than the PSM itself. The CPR-Valve material is usually comprised of a simple sugar, but can take many forms depending on the needs of the system. The placement of the CPR-Valve in physical contact with the bottom surface of the PSM causes the liquid (plasma) within the PSM to flow into the CPR-Valve under capillary action. Once plasma is within the CPR-Valve, the soluble material dissolves, releasing the plasma as a free-standing drop into the space between the PSM and the base of the plasma pooling area. In this fashion, no external pressure is applied in order for the PSM's inherent breakthrough pressure to be overcome. The droplet of plasma forms a connection or meniscus between the bottom surface of the PSM and the base of the pooling area. The presence of plasma within this space and in contact with the bottom surface of the PSM allows the plasma to continue to flow through the bottom surface of the PSM as it wicks along the space, with the meniscus being drawn forward due to capillary action, eliminating the capillary barriers retaining additional plasma within the small bottom pores of the PSM. This contributes to additional flow of plasma into the pooling area and causes the meniscus to spread further. The capillary force caused by the meniscus bound by the hydrophilic surfaces of the bottom surface of the PSM and base material continues to draw meniscus forward, breaking additional capillary barriers as it spreads. In this manner the entire surface area of the PSM can be recruited to separate plasma, not just in the area of the placement of the CPR-Valve.

[0024] *FIG. 1* illustrates a typical geometry profile of the PSM **100**, CPR-Valve **200** and base material **310**. The spread or movement of the meniscus **400** formed between the PSM and base material leading to a point **420** where the separated plasma may be collected. *FIG. 2* illustrates how a capillary tube **600** can be introduced into the plasma pooling space **410** through a hole **450** in the bottom of the base material **310**. Plasma will flow into the capillary by capillary force provided the physical and material parameters of the capillary tube satisfy the conditions of continued capillary flow, to be discussed more later in this disclosure.

[0025] Flow through the PSM will continue until all plasma available for collection has passed through, until the pores of the PSM become blocked by cellular components of the

whole blood or until the lagging end of flow generates a higher capillary barrier than is present at the leading end of flow. However, if flow does not continue through the PSM, it is still possible to collect, or extract, all plasma that has pooled under the PSM. This is possible by placing a venting duct **330** in the system, *FIG. 2*, which allows air to pass into the plasma pooling space **410** as plasma is drawn out of the same space and into the capillary tube **600**. The vent **330** acts as a capillary barrier and does not allow plasma to exit the plasma pooling area **410** under normal operating conditions. Lack of venting would generate a vacuum back pressure, which would prevent any additional plasma from being collected, except what may be pulled through the PSM by the capillary forces of the capillary itself, in excess of the volume of the plasma pooling area.

[0026] The strategic placement of the vent **330** will also allow the region under the PSM, where the original CPR-Valve **200** was located, to be bypassed while plasma is being collected from the plasma pooling area **410**. This causes all, or the majority, of dissolved soluble matrix of which the CPR-Valve is comprised, to remain in the plasma pooling area and not be passed into the capillary tube **600**.

[0027] By strategic placement of the CPR-Valve, vent, and capillary output, a system can be produced that reliably and repeatedly allows for plasma to be extracted from whole blood, fill a pre-defined space or channel, defined by the geometry of the space walls **320**, top **100** and base **310**, without trapping bubbles, and deliver the extracted plasma into a capillary tube **600**, which can be removed and used to dispense the collected plasma anywhere it is needed.

[0028] Capillary Pipette: The physical and material parameters that are needed for plasma to enter the inserted capillary tube under passive capillary forces are defined by the capillary force equation shown here:

$$P = - \frac{2\sigma \cos \theta}{r}$$

where: P Capillary Pressure
 r radius of pore or flow channel
 θ contact angle of channel or membrane material
 σ surface tension of liquid

[0029] A negative pressure is similar to a suction force that draws liquid into the system. A contact angle greater than 90° represents a hydrophobic material, and the resulting capillary pressure turns positive, indicating a positive force is required to push liquid into the system.

[0030] At the point where the capillary tube enters the plasma pooling area, an interface exists between two different geometries. In order for plasma to flow into the capillary tube, the capillary pressure, or capillarity, of the geometry and material of the capillary tube must be greater than the capillarity of the geometry and materials comprising the plasma pooling area. In other words, the difference between P_{cap} (or just P_c) and P_{pool} (or just P_p) must remain negative, as is illustrated by this equation:

$$\Delta P = P_c(\sigma_c, \theta_c, r_c) - P_p(\sigma_p, \theta_p, r_p) = \frac{2\sigma_p \cos \theta_p}{r_p} - \frac{2\sigma_c \cos \theta_c}{r_c}$$

[0031] The surface tension (σ) between the liquid (plasma) and air does not change from one geometry to the next, so $\sigma_c = \sigma_p$, which allows the equation to be simplified to:

$$\Delta P / 2\sigma = \frac{\cos \theta_p}{r_p} - \frac{\cos \theta_c}{r_c}$$

[0032] The geometry of the flow channel in the capillary tube is cylindrical, with a known radius r_c , but the geometry of the pooling area is rectangular, requiring an effective hydraulic radius to be calculated, based on the equation:

$$r_p = \frac{ab}{a+b}$$

where: r_p Effective hydraulic radius of the pooling area
 a height of pooling area flow channel
 b width of pooling area flow channel

[0033] For example, in a case, such as where the height of the pooling area flow channel is 170 μ m, and the width is 1250 μ m, the effective radius can be calculated to be approximately 150 μ m. In the case where the capillary tube also has a radius of approximately 150 μ m, the equation of paragraph 25 can be simplified to:

$$\Delta P r / 2\sigma = \cos \theta_p - \cos \theta_c$$

[0034] If the material of the pooling area is mainly derived of hydrophilic plastics, which may have a contact angle (θ_p) of around 75°, and the capillary tube is comprised of glass, with a contact angle (θ_c) of around 15°, $\cos(75^\circ) = 0.26$ and $\cos(15^\circ) = 0.97$, the difference is negative, allowing flow to continue into the capillary tube.

[0035] In the case where the radii of the two geometries are not approximately the same, and it is desired to derive an equation that clarifies what the relationship between r_c and r_p should

be, in order for the capillary pressure at the junction to remain negative, the following relationship can be derived from the equation of paragraph 31, namely:

$$r_p \cos \theta_c > r_c \cos \theta_p$$

[0036] Using the same contact angles as before, and rearranging to emphasize the desired radius of the capillary tube, we obtain:

$$r_c < 3.7r_p$$

[0037] While this relationship is useful to keep in mind, it does not take into account some very critical issues associated with microfluidics, capillary forces, and commercially viable manufacturing and assembly issues in general. These issues include variability in material properties, surface roughness, and in particular, precise alignment between surfaces and junctions.

[0038] Considering the illustration shown in *FIG. 3*, an input metering capillary **500** is used to deliver a minimum volume of whole blood to the PSM **100**. A cover **550** is also used to facilitate wicking of the blood across the whole PSM, rather than just pooling nearest to the input capillary. The alignment between the input capillary **500**, the cover **550**, and PSM **100** is important to ensure blood reaches the PSM and can be distributed. The blood in the capillary will also be subject to gravity, in addition to capillary forces, such that, if the capillary tube does not fully reach the PSM, the blood in the capillary tube may extend slightly past the end of the capillary tube to aid in bridging any gap.

[0039] However, if the capillary tube extends too far past the bottom surface of the cover, it may become imbedded into the PSM, preventing proper wetting of the PSM and adequate pooling of blood across the whole surface area of the PSM to facilitate even plasma extraction.

[0040] Also to facilitate even distribution of the input blood sample, an input vent **510** is needed. As blood covers the PSM, air in the space between the PSM and the cover and air within the PSM must be vented out. This may take place by air passing through the plasma pooling area **410** and out through the output capillary pipette **650**, but it is more reliable to have a separate vent **510**, either in the cover, as is illustrated in *FIG. 3*, or in the base, as is illustrated in *FIG. 4*. In either case, it is useful for the vent to be placed in a position where blood or plasma does not leak out during normal device operation. Also, as is illustrated in *FIG. 4* and again in *FIG. 7*, it may be useful for the vent to be offset slightly from the location of the PSM **100** by placing a slot or notch **515** in the spacer surrounding the PSM **322** and **323** so that air

may vent out all around the PSM and not be obstructed in any fashion by the input whole blood that covers the PSM.

[0041] To operate the device, the input capillary tube **500** should be slightly inclined with the body of the separation device slightly higher than the tip of the input capillary tube. The input is touched to a drop of blood that has formed on the surface of a finger previously punctured with a lancet or needle. The capillary tube should continue to draw blood into it until it reaches the end of the tube, which can be visually observed, or until it reaches the PSM itself, which is also visibly observable. At this time the device should be held upright to facilitate wicking of the blood across the whole upper surface of the PSM. Not all blood may leave the input capillary tube initially, but may slowly move down as the PSM saturates and plasma is extracted through the membrane.

[0042] If the input capillary tube is declined during filling, the blood in the tube may prematurely separate from the droplet on the finger and flow, by gravity, down the capillary tube. Attempting to add more blood may trap a bubble, preventing further flow.

[0043] As the plasma collects in the pooling area **410**, it will spread and move toward an opening **450** which is the entrance of a capillary pipette **650** that is inserted through the base of the device. Rather than just a capillary tube, the capillary pipette **650** is illustrated in *FIGs 3 – 4 and 6 - 8*, which is a capillary tube **600** modified with a plastic sheath for protection with finger gripping points **630**, a squeeze bulb **670**, a vent in the squeeze bulb **610**, and a fitting **620** and **625** that allows for easy removal of the capillary pipette for dispensing the collected plasma where it is needed. The capillary tube can be made of glass, plastic, metal or other material that is hydrophilic or can be rendered suitably hydrophilic for the purpose of drawing plasma in by passive capillary forces. The upper surface of the capillary **600** within the capillary pipette **650** should be flush with the entrance of the hole or via **450** in the plasma pooling areas **410**.

[0044] Although some metering of the plasma volume takes place due to the geometry of the pooling area, the exact volume of plasma collected into the capillary pipette can be precisely controlled by the geometry of the internal capillary **600** itself. Plasma enters this tube within the capillary pipette and is held by capillary stop junctions at its inlet and outlet. Air is vented out of the capillary through the small hole **610** in the pipette's squeeze bulb **670**. The pipette can be removed from the body of the device using the finger grips **630**, not by holding on to the squeeze bulb, and gently twisting the pipette while pulling it away from the body of the

device. Once separated, the pipette can be moved around gently without fear of plasma exiting or dripping from it.

[0045] To dispense, the tip of the pipette is placed at the desired location of dispensing, the bulb is squeezed, with the vent hole **610** covered, and the plasma is then forced out of the internal capillary **600**.

[0046] *FIG. 3* illustrates a single, straight channel for the plasma pooling area **410**, and a friction fitting for the capillary pipette **620** and **625**. The body of the plasma extraction device is either thermoformed or injection molded and sealed or pinched round the edges including the edge of the PSM **100**. *FIG. 4* illustrates a laminated version of the plasma extraction device, with the plasma pooling area or channel **410** formed in an adhesive layer **320** in the shape of a 'U'. The capillary pipette **650** is held in place with a thin adhesive layer **625**, and has more pronounced finger grips **630** to facilitate removal. A screw-type, or luer fitting **620** can also be used to attach the capillary pipette to the body of the device, in addition to friction or adhesive. Instead of pinching or compressing the PSM **100** between the cover and base material as shown in *FIG. 3*, in *FIG. 4* the PSM **100** is held within a cut-out section of a spacer comprised of plastic **323** and adhesive **322** layers, and rests on the adhesive layer **320** that forms the channels of the plasma collection area.

[0047] In *FIG.s 3* and *4* the internal alignment between the plasma pooling area **410** and output capillary pipette **650** is critical to proper device function. This alignment can easily be achieved using standard device design and assembly methods. These include using robust, precision luer lock fittings, or thin adhesive layers, with proper quality controls in place.

[0048] Another important element in device usage is to ensure plasma extraction and filling of the capillary pipette is complete before removal of the capillary pipette. This can be done by placing a contrasting agent or mark near the end of the capillary pipette that generates a visible difference between filled and unfilled capillaries. This could be a very thin and readily soluble inert dye placed within the capillary itself. During manufacturing of the device the dye could be inserted a short distance at the distal end of the capillary and then blown out once it has partially dried so that it does not clog or block flow of plasma filling the pipette, but leaves a light colored film that disappears once plasma has filled the capillary. Another method may be to scratch the inside of the distal end of the capillary with a diamond-tip bit, or similar device. The scratch marks would disappear when the capillary is filled with plasma. Alternatively, the inside surface of the distal end of the capillary could be coated with a hydrophobic film so that it is not filled. The difference between a filled and unfilled portion of the capillary, when they

are side by side, can be recognized. Finally, if the capillary is held vertically, a very small volume of plasma may extend past the end of the capillary, showing that it is filled.

[0049] Direct Dispensing: In a previous example, the radius of the capillary was suggested to be 150 μ m. If the desired volume the capillary pipette is to collect and dispense is 5 μ L of plasma, then its required length can be easily determined by the relationship between volume and length of a cylinder with a known radius, as illustrated by the equation:

$$Length_c = \frac{Vol}{\pi r_c^2}$$

where: r_c Radius of the capillary

Vol Desired capillary collection volume

[0050] For the case cited, Vol = 5 μ L, r_c = 150 μ m, then $Length_c$ = 70.8mm, or 2.8 inches. In the design illustrated in **FIG. 4**, this $Length_c$ represents the length of the capillary **600** inside narrow diameter portion of the capillary pipette **650**. The capillary can extend into the bulb region, but the minimum length of the entire capillary pipette will need to be at least 70.8mm. Such a long length of an unsupported glass member begins to introduce fragility into the device design.

[0051] Consider further a case when a capillary tube of the same radius is used, but the desired collection volume is 10 μ L rather than 5 μ L. This requires a capillary of double the previous length, or 141mm. It is possible the radius of the capillary tube can be increased to allow for a shorter capillary, Using the equation of paragraph 50, in order to maintain a maximum capillary length of 70.8mm, r_c will need to be 212 μ m to accommodate a volume of 10 μ L. Fortunately this still satisfies the condition described by the equation in paragraph 35, using the same materials and geometry as used previously, with an effective r_p of 150 μ m. However, this requires the alignment of the output capillary to be much more precise in order to ensure reliable operation, which may be beyond the manufacturing constraints that allow a cost effective device to be produced.

[0052] An alternative solution to the very long capillary tube or high precision manufacturing and assembly needs, is illustrated in **FIG. 5**. In this design the collected plasma is dispensed directly from the body of the device, rather than collected and dispensed from a removable capillary pipette.

[0053] The alignment challenges are much more relaxed because it is not intended for plasma to enter the squeeze bulb **770** or dispensing tip **870** regions under capillary forces because the interface to these regions are designed to represent capillary barriers which are not pushed past

during plasma filling of the pooling or collection channel **410**. Rather, positive pressure is applied by squeezing the bulb **770** to dispense plasma out of the pooling area, through the tip **870** and into an external receiving area.

[0054] An input capillary cover or cap **501** is needed to ensure any remaining whole blood is not ejected out through the input capillary **500** when the squeeze bulb is actuated. The suspended or unsupported area of the PSM **100**, directly above the pooling area, may act as a type of movable diaphragm when the squeeze bulb is actuated. Care is needed to prevent this movement from causing leakage or ejection through the input capillary **500**. The cap **501** would be put in place after the plasma has filled the plasma pooling area and before the squeeze bulb is actuated.

[0055] Aliquot Plasma: *FIG. 6* illustrates a design where a single input volume can be aliquoted into two output volumes. This provides another alternative to preventing excessively long output capillary pipettes, which can be accomplished by splitting the output into two different capillary pipettes **651** and **652**, of either equal or unequal volumes. However, the primary advantage of this design is to enable dispensing two plasma volumes into two different destinations, but with only a single input requirement.

[0056] This method requires the two pooling areas **411** and **412** to be distinct from each other, including two separate CPR-valves **201** and **202**. However, they may share a common vent **330** because the plasma does not connect or span across the vent in the design illustrated. Sharing a single channel (without a vent separating the two aliquots) and/or sharing a single CPR-valve leads to irregular and non-repeatable behavior, and does not ensure the two aliquots are divided repeatedly and reliably into the desired volumes.

[0057] Plasma Flow Within the PSM: Many of the membranes developed for plasma separation were initially developed for lateral flow applications, such as in lateral flow immuno-assays. Hence, the separated plasma can actually flow quite well within the lateral dimensions of the PSM. Referring to *FIG. 4*, it has been observed on numerous occasions that the output capillary pipette **650** is able to completely fill before any air enters into the plasma pooling channel **410** through the vent **330**. This can only be explained by plasma flowing laterally from any point on the PSM **100** and emptying into the channel **410** which feeds into the output capillary **600**, rather than the pooling channel filling once and emptying once into the capillary.

[0058] This means that, at least in some cases, the plasma pooling channel **410** under the PSM is not effective in metering the volume of plasma passed downstream. Fortunately, the

output is effectively metered by the output capillary **600**. However, if the plasma pooling channel is not useful for metering, it can be eliminated or modified to serve other useful functions. Three modifications that can be made include 1) eliminating the output venting duct to simplify manufacturing; 2) making the pooling channel shorter to facilitate plasma reaching the output capillary more quickly; and, 3) making the adhesive layer thicker to allow for a larger diameter output capillary to be used while still retaining sufficient capillary forces needed to draw plasma into the output capillary.

[0059] Regarding a thicker adhesive layer, or greater distance between the bottom surface of the PSM and top surface of the base of the device, if this distance is too large it can become difficult for the meniscus to form between these two surfaces. However, assuming a meniscus does form, the larger space also makes the meniscus move more slowly forward. This is the reason the pooling channel can be shortened, so the more slowly advancing meniscus still reaches the output capillary within a reasonably short period of time.

[0060] If the space between the two surfaces is greater, the effective hydraulic radius discussed in paragraphs 32-36 will be larger, which means the allowable radius of the output capillary can be larger, meaning its length shortened for the same metered volume.

[0061] Metering by the volume of the pooling channel under the PSM can still be achieved if the speed of filling of the output capillary tube, or other output structure, exceeds the speed of lateral flow of the plasma to fill, or re-fill, the pooling channel. But, in the case of an automatic, stand-alone centrifuge replacement device, with an output capillary pipette, it is better for the output capillary to control metering due to the 3 benefits described in paragraph 58. An example of a device using these three benefits is illustrated in *FIG. 7*, where the normal metering plasma pooling channel **410** of earlier figures is replaced with a shorter, deeper and non-metering plasma pooling channel **413**, and the venting duct **330** of previous figures is no longer used.

[0062] CPR-Valve Double Duty: Despite the three benefits described in paragraph 58, the desired processing and collection volume of plasma may be far larger than can be accommodated using thicker adhesives, shorter pooling channels or other means of balancing the capillary force equations discussed previously. According to the equation discussed in paragraph 36, and using the same materials and geometries mentioned in that case, if the output capillary has a radius that is larger than 3.7 times the effective hydraulic radius of the plasma pooling channel, then the interface between the output capillary and the plasma pooling channel represents a capillary stop junction and the plasma will not enter into the output capillary.

[0063] However, the whole point of this disclosure and function of the CPR-Valve or mechanism, is to not be limited by capillary stop junctions or other capillary barriers that may exist in certain systems. As is illustrated in *FIG. 8*, the CPR-Valve **200** can be designed to serve a dual purpose, both to eliminate the breakthrough pressure of the PSM **100**, and to simultaneously overcome the capillary stop junction present at the inlet of the output capillary **600**.

[0064] Both the illustration in *FIG. 8*, and further detail shown in *FIG. 9*, the CPR-Valve **200** is placed between the output capillary **600** and the PSM **100**, with a portion of the CPR-Valve extending past the output capillary **600** to lie between the PSM **100** and base **310**. The CPR-Valve first overcomes the breakthrough pressure of the PSM, causes the meniscus of the pooling plasma to spread radially outward through the channels, spokes or arms of the plasma pooling area **413** extending from the center and reaching out to the edges of the PSM, and at the same time introduces the plasma into the output capillary. As in the short channel design illustrated in *FIG. 7*, this design relies on plasma flowing laterally in the PSM before it empties into the collection channels. The number of spokes or channels can be optimized depending on the desired speed of collection, surface area of the PSM, device fabrication, assembly and reliability issues.

[0065] Timing of the spreading plasma and its introduction into the output capillary is important. If the thickness of the adhesive **320**, or channel depth between the PSM **100** and base **310**, is kept very small or thin such as between 25-50 μ m, and the width of each channel **413** is kept small, such as less than 1 mm, the meniscus will spread outward rapidly. Although a larger number of branches or spokes could increase the speed of filling the output capillary, it also increases the chance of one branch not filling properly and trapping a bubble instead. If the CPR-Valve **200** introducing plasma into the output capillary **600** is slightly thicker, or denser than it is outside the capillary where it contributes to overcoming the PSM breakthrough pressure, then it will take a slightly longer time for the plasma to be introduced into the output capillary **600**. It is important that sufficient plasma has passed into the pooling space or branches **413** and extends to the pooling area vents **331**, before the plasma is drawn into the output capillary **600**, so the output capillary does not draw an air bubble into it rather than plasma. In this case the vents **331** shown in *FIG. 8* are not used to introduce air into the pooling area as plasma enters the output capillary, as is the case for vents **330** shown in previous figures, but rather to vent air out of the pooling channels **413** as they fill, beginning at the center of the device where the CPV-Valve **200** is located, and expanding radially outward. If plasma reaches

the vents **331**, air will not re-enter through the vent into the pooling channels **413** because the adhesive layer **320** is so thin, a strong capillary junction exists at the point of the vent **331**, and air will not enter. In this case, the total volume of plasma in the pooling channels **413** will contribute to the dead volume of the system because it cannot be collected into the output capillary.

[0066] Initially plasma is drawn into the output capillary by capillary force. But, depending on the geometry and volume of the output capillary, at some point the weight of the liquid column (if the device is held upright) will begin to act as a suction source that will draw an air bubble into the capillary **600** if plasma in the channels **413** have not yet reached the output vents **331**. This appears to become a factor when the liquid column height in the output capillary **600** approaches 20mm or greater. To prevent this from happening, the pooling space or channels under the PSM should be filled with plasma rapidly without trapping bubbles. Alternatively, the device could be placed on its side to minimize any suction pressure that is generated by the column of plasma in the output capillary. In this case the squeeze bulb **670** should be resting on the support surface, such as a table, with the inlet of the capillary, within the device, slightly higher in elevation than the squeeze bulb. This will allow capillary forces to continue to function properly and gravitation forces to only be slightly additive, but weaker than if the device is in a vertical position.

[0067] In the case where the CPR-Valve **200** is between the output capillary **600** and the PSM **100**, if the soluble material comprising the CPR-Valve is dyed, it can be observed that the material is first drawn radially outward by the radially expanding meniscus, but then is it drawn inward by the flow of plasma entering the output capillary. In contrast to the previous design where most or all of the CPR-Valve material can be excluded from the collected plasma volume, in the current design *FIG. 8 and 9* the CPR-Valve material, either entirely or in large part, will be drawn into the output capillary rather than cut-off from collection, as has been described previously. In this case it is of more importance for the material comprising the CPR-Valve to not be an interferent in any downstream process, such as in biomarker detection, than in the case when all or the majority of dissolved CPR material is excluded from collection.

[0068] Integrated Reagent: As has been mentioned, in the design illustrated in *FIG.s 8 and 9*, all or the majority of the material comprising the CPR-Valve **200** will be collected by the output capillary **600**. Thus, the material should not interfere in downstream processes, and since it is reliably and repeatedly passed downstream, the CPR-Valve can be comprised of materials

important to downstream processing. This is illustrated in *FIG. 10* where a reagent disk **250** is located between the CPR-Valve **200** and the output capillary **600**.

[0069] Instead of being 2 different structures or materials, the CPR-Valve **200** and reagent disk **250** can also be the same structure and material, depending on the needs of the system. In this case the plasma separation device is not necessarily an independent stand-alone centrifuge replacement tool but, due to the presence of a specific reagent that is closely associated with a specific application or diagnostic test where the reagent is used, it becomes an integral component of a specific diagnostic application or test. The reagent **250** should also be present in excess of the minimum needs of the application, to ensure adequate reagent is present in the downstream system if not all of the reagent is collected in the output capillary **600**. A common example of this is conjugate reagent being present in excess for downstream lateral flow devices.

[0070] In many diagnostic applications reagents are present in the form of lyophilized beads or pellets. It is possible they can be in the form of a disk that is in contact with the CPR-Valve **200**. It is also possible the reagent can be used as a CPR-Valve. The primary requirements of a CPR-Valve are that it possesses high capillarity in dry form, to draw liquid out of the PSM, that it facilitates the generation of a meniscus between the PSM and base of the device, and that it is readily soluble in the filtrate or plasma without increasing the filtrate or plasma's viscosity to any great degree. Some characteristics of lyophilized materials may not allow it to be used as a CPR-Valve, and may complicate the introduction of liquid into the output capillary, such as very rapid if not explosive dissolution or disintegration in the presence of liquid, which may complicate meniscus formation or inject bubbles into the output capillary. If this is the case the reagent **250** could be placed near the CPR-Valve **200** and/or output capillary **600**, rather than used instead of the CPR-Valve or in contact with the output capillary. Even in this condition it is very likely the majority of the reagent will be collected into the output capillary during the separation and collection process.

[0071] Surface Area, Hematocrit and Input and Output Volumes: Because most PSMs are asymmetric size exclusion filters, ranging from large pore size at the top to smaller pore size at the bottom, if sufficient blood is passed through them, they will eventually clog with cells preventing further plasma separation or extraction. Because of this, commercial PSMs are often rated in volume of input blood per square centimeter of surface area of the filter, or membrane.

[0072] For example, the GR grade of the Pall Vivid PSM states 40-50 μ L of whole blood input per square centimeter of membrane surface area. However, in the laminated designs

illustrated in *FIGs. 2, 4 – 8*, a large portion of the bottom surface of the PSM is blocked by adhesive **320**, which is used to support the membrane and to define the geometry of the plasma pooling area **410**, **411**, **412** or **413**. Unfortunately, however, this does not mean that the corresponding upper surface of the PSM does not need to be covered, which would reduce the total volume of whole blood required. Experimental analysis has shown that the entire upper surface area and total depth of the PSM must be saturated with the input whole blood in order for the devices to function properly. This reduces the efficiency of separation. In a thermoformed or injection molded design, however, it is possible to pinch or squeeze-off a portion of the upper surface area and corresponding depth or thickness of the PSM, which would allow an upper surface area to approximately equal the top of the plasma pooling area. This would increase the efficiency of the system.

[0073] Another factor effecting potential plasma volume is the hematocrit of the input whole blood sample. Hematocrit is the ratio of whole blood volume to packed cellular components of the blood. A low hematocrit represents a low cellular component of blood and larger liquid, or plasma component. A high hematocrit represents a higher cellular component and lower liquid or plasma component. Typical physiological ranges of hematocrit variability among healthy individuals is between 38-55%, meaning a maximum volume of 62 μ L of plasma could be extracted from an individual with a hematocrit of 38%, if the starting whole blood volume were 100 μ L, but only 50 μ L if their hematocrit were 50%. In addition, unhealthy individuals, or people acclimated to extreme conditions, such as high altitude, infants, and other sub-groups may have hematocrit ranges much broader than this. Hematocrit variability, if not accounted for, can represent a significant variation and source of error in blood-based diagnostics, where the measurement of biomarkers and their physiological significance is measured in units of plasma or serum and not whole blood.

[0074] In order to ensure proper device function, and taking into account dead volume, surface area specifications, blood or plasma retained with the PSM or overall efficiency in separation of the PSM, and potential hematocrit variability, a device that specifies a fixed and accurate plasma extraction, metering and dispensing capability will, by its nature, be inefficient in its ability to collect the total volume of plasma available in a sample.

[0075] Depending on the overall design of the devices illustrated in the figures, and depending on whether they are molded, thermoformed or laminated, and depending on the allowable range of hematocrit that can be accommodated for, the devices disclosed in this filing are capable of extracting approximately 1 μ L of plasma from every 3 to 6 μ L of whole blood input.

[0076] Another embodiment of the technology is illustrated in *FIG. 11*, where the efficiency of the system can be improved by having an extension **415** of the plasma pooling area **410** that extends past the boundary of the PSM **100**. The depth or thickness of the pooling area cannot be too thick because of the difficulty in establishing a meniscus between the upper and lower surfaces, and because of the need for capillary forces to help drive the meniscus, which capillary forces may become too weak if the thickness or depth of the pooling area **410** becomes too large, such as greater than 300 μ m. However, a microchannel or extension **415** with a higher capillary force than the pooling area **410** directly under the PSM **100** can serve to draw some of the plasma out from under the PSM, which is replaced by more plasma passing through the PSM. The interface to the output capillary **600** could then connect with this extension **415**. However, in this case the capillarity of the output capillary **600** must be higher than the capillarity of the extension **415**, rather than the capillarity of the pooling area **410** under the PSM **100**.

[0077] Input Volume Metering: As has been mentioned, depending on a capillary tube's geometry (e.g. inner-diameter) and composition (e.g. glass or plastic), and the liquid that it holds (e.g. blood) which define its capillarity, gravity can have an effect on the position or movement of liquid inside. For example, a small amount of plasma can extend past the end of the output capillary, signaling it is full. This is due to the weight of the liquid pushing on the meniscus, and the fact that at the rim and edges of the capillary may still have strong capillary forces, or high surface energy, allowing the plasma to migrate slowly down and out when, theoretically, the abrupt end of the capillary should represent a stop-junction which should prevent any further movement of the plasma. This creeping outward is slowed or stopped when the capillary is held in a horizontal position, indicating gravity has an effect on the liquid in the capillary.

[0078] Factors that influence the spread of liquid out of the capillary include the height of the column of liquid, the ID (inner-diameter) of the capillary, its density which, together with ID and column height indicate the mass of the liquid, the thickness of the glass capillary walls and the angle of the capillary with respect to gravity.

[0079] For example, it has been observed that, when held vertically, the blood within a 1mm ID glass hematocrit tube will extend past the bottom of the tube by about 1mm if the column of blood within the tube is at least 30mm in height. But, it will only extend past the bottom of the tube by about 0.5mm if the column height is reduced to about 25mm. Also, the edges of the extension of the meniscus past the end of the tube can be seen to migrate from being

constrained to the inner walls of the capillary to move to the outer edge of the capillary when the column is higher.

[0080] If a first capillary tube, where the sample is introduced, is held in a slightly inclined position such that the distal end is slightly elevated above the proximal end, between 0.5 to 30 degrees up from the horizontal, the sample should fill the tube automatically by capillary force and stop at the distal end. If the distal end is enclosed in another capillary tube that has an ID (inner-diameter) that tightly fits with the OD (outer diameter) of the first tube, the capillary stop junction at the distal end of the first tube should still stop the flow of liquid filling it at its proximal end. Even though it is enclosed in a second tube, the ID of the flow channel still increases sufficiently to generate a capillary stop junction.

[0081] If, however, once the first tube fills to its end point, both tubes are held upright or vertical, depending on the length of the first tube, the weight of liquid inside it can be sufficient to draw it past its stop junction until the extended meniscus contacts the ID of the second tube, causing it to move forward, eliminating the stop junction, and allowing liquid to move forward. In this case the weight of the liquid in the column breaks the capillary stop junctions at both the inlet and outlet of the first capillary tube.

[0082] This situation is illustrated in *FIG. 12 a* and *b* where the distal capillary stop junction **580** of the first capillary tube **500** can be used to precisely meter the input volume of liquid (blood) **900** that is loaded into the first tube as it is in its loading position, with the distal end slightly elevated above the input. However, when the system is held upright the weight of the sample **900** can push it past this stop junction **580** and into the second tube **590**, which leads to the downstream device which must have appropriate properties to draw in the metered input volume, such as by having sufficient capillarity to draw liquid out of the first **500** and second **590** capillary tubes, in this case a PSM **100**.

[0083] This design can more precisely meter the input of a system where more precise metering is important. In the design mentioned previously only a minimum volume of input is ensured, but the maximum was not controlled. In this new design the minimum and maximum are controlled, by filling to the stop junction **580** of the first capillary **500**, which can be visibly observed. An example of when input metering is more critical is when the plasma extraction device disclosed herein is optimized for function as a hematocrit measurement device, where both input and output are measured.

[0084] Although a few exemplary embodiments of this invention have been described, those skilled in the art will readily appreciate that many modifications are possible in the exemplary

embodiments without materially departing from the novel teachings and advantages of this invention. Accordingly, all such modifications are intended to be included within the scope of this invention as defined in the claims. Therefore, it is to be understood that the foregoing is illustrative of the present invention and is not to be construed as limited to the specific embodiments disclosed, and that modifications to the disclosed embodiments, as well as other embodiments, are intended to be included within the scope of the appended claims. The invention is defined by the following claims, with equivalents of the claims to be included therein.

CLAIMSWhat is claimed is:

1. A method of producing a filtrate available for collection, wherein the breakthrough pressure of a filtration membrane is overcome by use of a soluble matrix placed in physical contact with the downstream surface of said membrane which draws said filtrate through said membrane passively, which soluble matrix then completely or partially dissolves in said filtrate, releasing said filtrate from being bound within said matrix and making said filtrate available for collection.
2. The method of Claim 1, wherein said collected filtrate is metered to at least one specific volume or aliquot, by allowing said filtrate to pass into at least one collection region of at least one known start point and at least one known end point, the volume or volumes enclosed within such collection regions being known, and the filtrate passing into said collection regions by passive capillary forces defined by the geometry and materials of which said at least one collection regions is comprised.
3. The method of Claim 1, wherein said collected filtrate is plasma or serum.
4. The method of Claim 2, wherein said collected and metered filtrate is plasma or serum.
5. The method of Claim 2, wherein said at least one known start point is the inlet to at least one capillary tube and the at least one known end point is the outlet of at least one capillary tube, the collected aliquot or volumes enclosed between said at least one start point and at least one end point are known and equal to the volumes enclosed by the geometries of said at least one capillary tube which is known.
6. The method of Claim 2, wherein said at least one known start point is a capillary barrier and the at least one known end point is a capillary barrier and said filtrate enters into and fills the space between said capillary barriers under passive capillary forces and is metered by the known volume of space between said capillary barriers.

7. The method of Claim 5, wherein said at least one capillary tube can be removed from said filtration membrane structure and used to transport, transfer or dispense said filtrate to any desired location.
8. The method of Claim 6, wherein at least one of said capillary barriers is comprised of an interface or connection to a dispensing tip and the at least one other capillary barriers in fluid communication with the capillary barrier connected with the dispensing tip is comprised of an interface to or connection with a structure designed to apply pneumatic pressure for dispensing said metered volume out of said dispensing tip.
9. The method of Claim 2, wherein at least one of said collection regions extends past the point of where said filtration membrane serves as one surface of the geometry which defines the volume of filtrate that is collected.
10. A process of delivering a metered volume of filtrate to a specific location or point, the process comprising:
 - a. providing a filtration device, comprising:
 - i. an inlet structure designed to ensure a minimum volume of liquid is loaded into the device;
 - ii. a filtration membrane;
 - iii. a filtrate collection structure of known volume; and
 - iv. a filtrate dispensing structure comprised of an outlet tip and a pneumatic pressure generating structure, both in fluid communication with said filtrate collection structure;
 - b. placing the inlet structure in fluid communication with liquid to be filtered;
 - c. allowing the inlet structure to fill to completion automatically driven by passive capillary forces;
 - d. allowing the filtration process to proceed to completion driven by passive capillary forces;
 - e. allowing the collection process to proceed to completion driven by passive capillary forces;
 - f. actuating the pneumatic pressure generating structure and placing the dispensing tip at the desired point of filtrate delivery.

11. The process of Claim 10, wherein said input liquid is blood and said filtrate is serum or plasma.
12. A method of overcoming the breakthrough pressure of a filtration membrane and simultaneously overcoming an inlet capillary barrier of a filtrate collection structure, by placing a soluble matrix in a space between a downstream surface of said membrane and an inlet of said filtrate collection structure, whereby a portion of said soluble matrix extends into the inlet of said filtrate collection structure and a portion of said soluble matrix is in physical contact between the downstream surface of said membrane and a base structure designed for holding said soluble matrix, filtrate collection structure and membrane in place.
13. A method of loading a chemical or reagent into a filtrate collection structure by placing said chemical or reagent in a fluid flow path between a soluble matrix designed to overcome the breakthrough pressure of a filtration membrane and the filtrate collection structure such that said chemical or reagent is drawn into said filtrate collection structure as said filtrate fills said collection structure.
14. A process of loading a precise volume of input liquid into a device, comprising:
 - a. providing a liquid collection structure comprising:
 - i. a first liquid delivery structure of specific dimensions, wherein the liquid holding volume of which equals the volume from the inlet to outlet of said first liquid delivery structure;
 - ii. an opening on an outlet of said first liquid delivery structure leading abruptly to a second liquid delivery structure, said opening representing a capillary barrier which stops flow from entering said second liquid delivery structure as the first liquid delivery structure is being filled;
 - iii. said second liquid delivery structure leading to a downstream liquid processing system; and
 - iv. said downstream liquid processing system possessing sufficiently high capillarity or liquid loading capacity so as to draw liquid out of said first and said second liquid delivery structures when said downstream liquid processing system is placed in fluid contact with said input liquid;

- b. placing the inlet of said first liquid delivery structure in fluid communication with liquid to be loaded;
 - c. holding the said first liquid delivery structure in an inclined position to allow loading of the liquid into the first liquid holding structure driven by passive capillary forces and allowing it to fill up to the point of the capillary barrier or outlet of said first liquid delivery; and
 - d. rotating the liquid collection structure to an upright position so as to allow the weight of loaded liquid to overcome the capillary barrier due to gravitational forces and allowing said liquid to flow through the second liquid delivery structure to the downstream liquid processing system.
15. The process of Claim 14, wherein said input liquid is blood and said filtrate is serum or plasma.

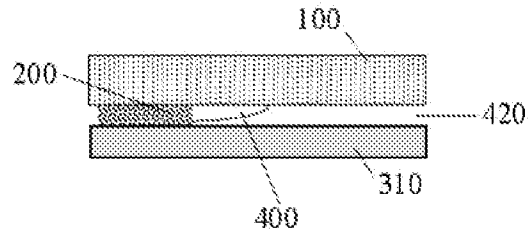


FIG. 1

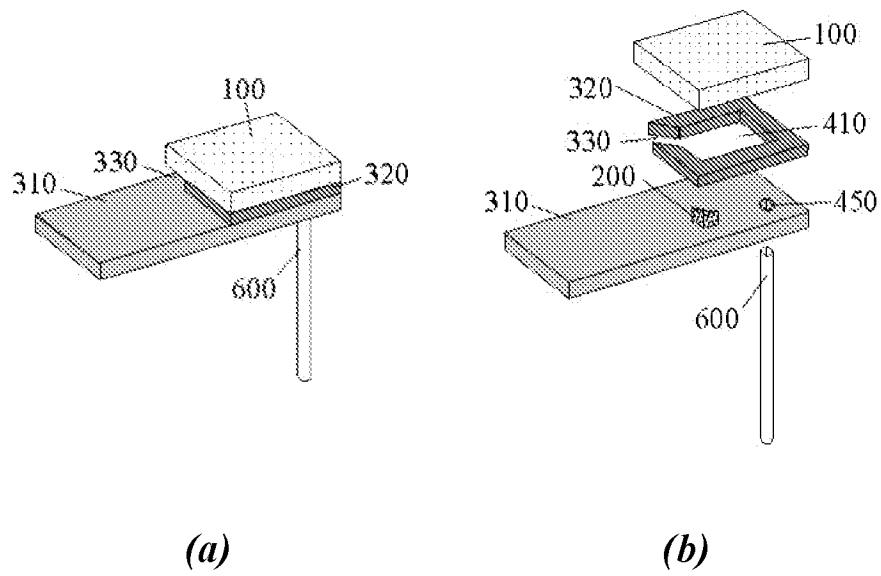


FIG. 2a & b

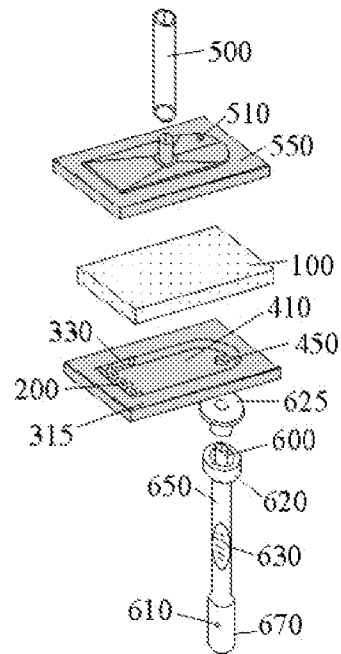
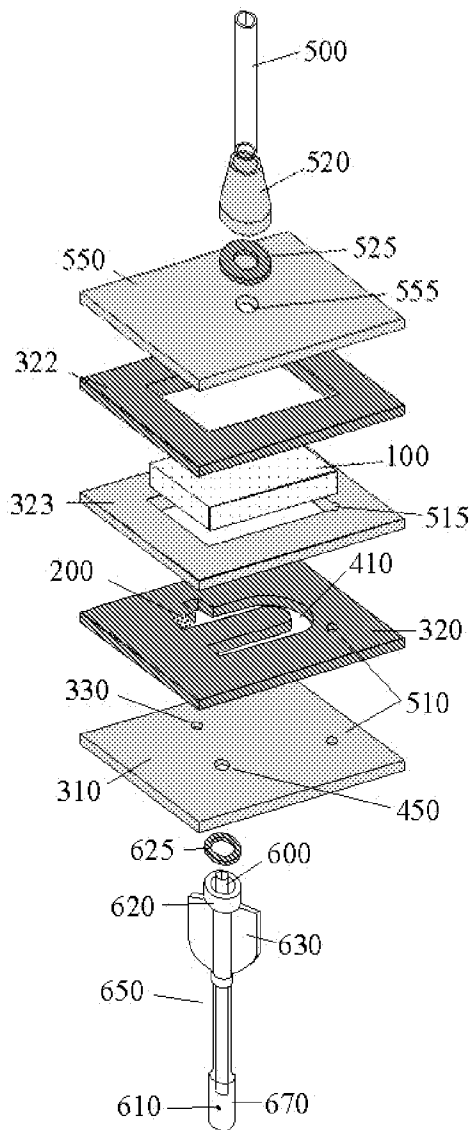


FIG. 3

**FIG. 4**

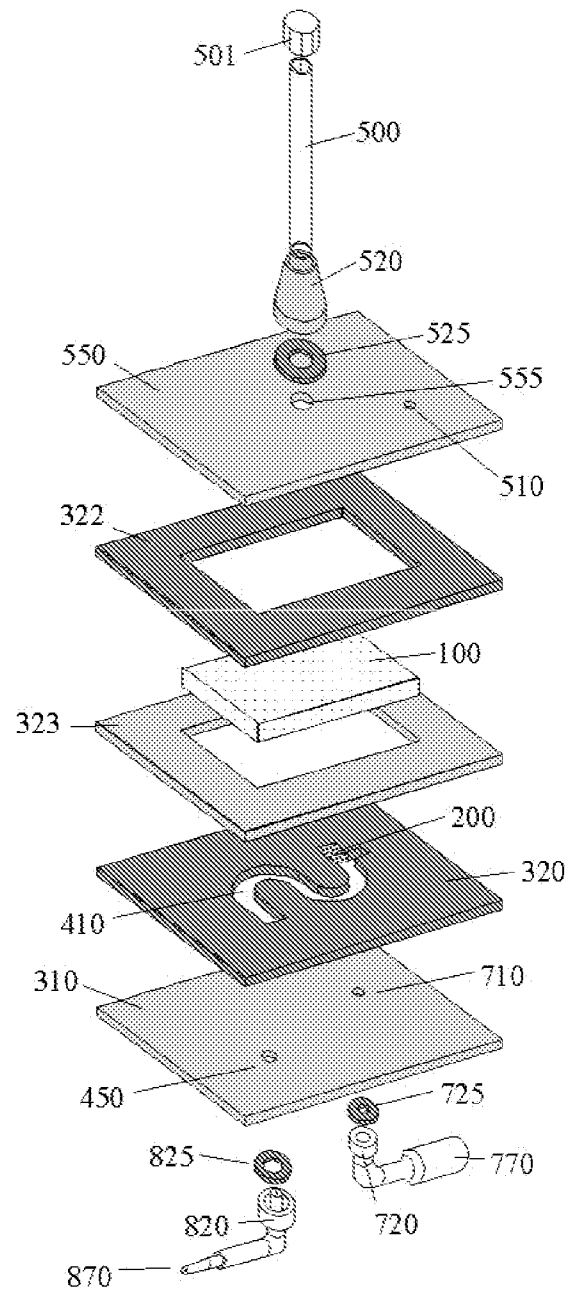


FIG. 5

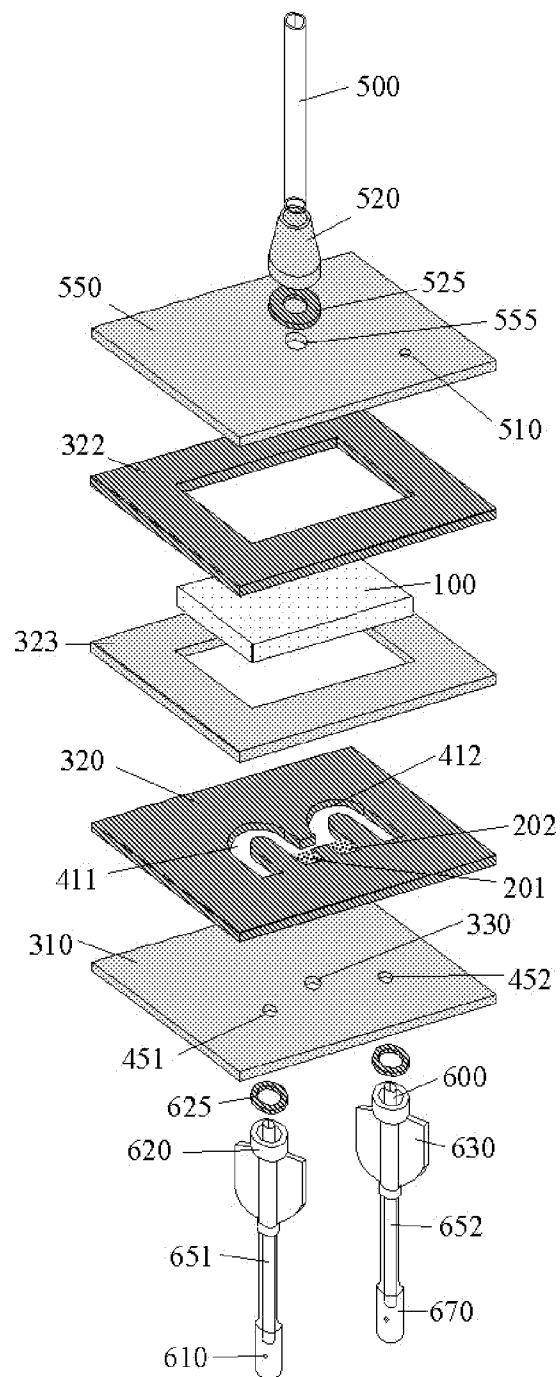
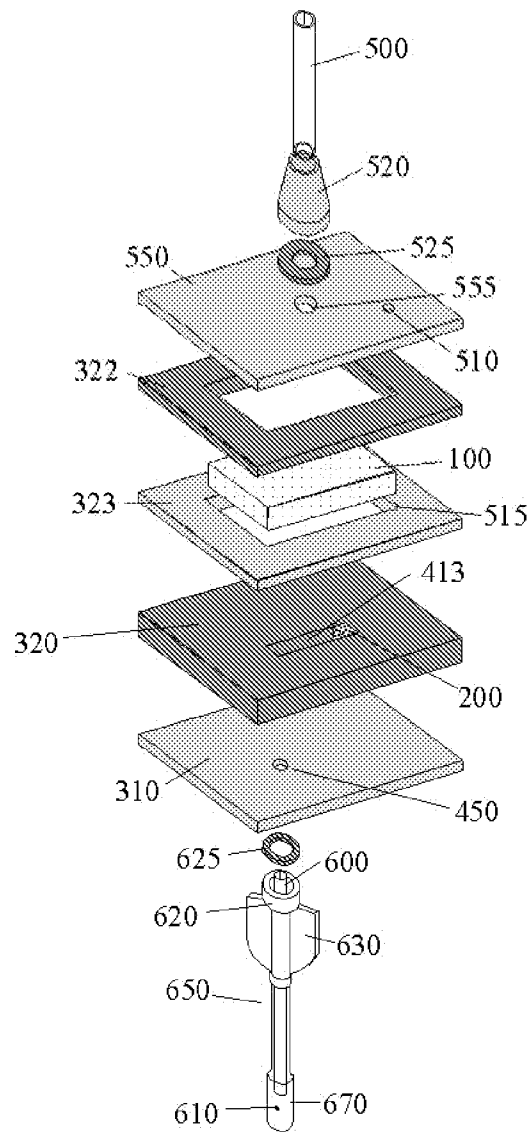


FIG. 6

**FIG. 7**

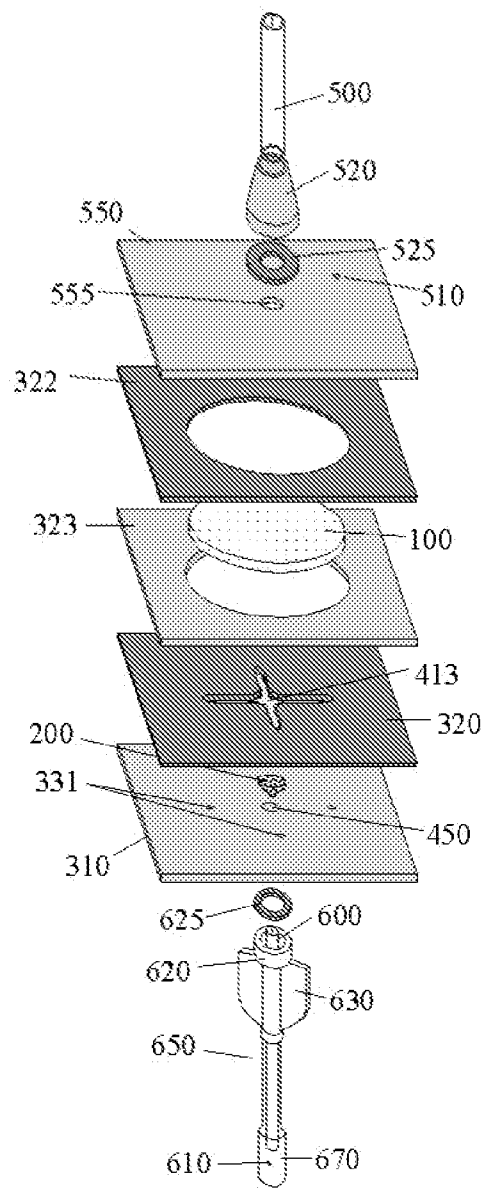


FIG. 8

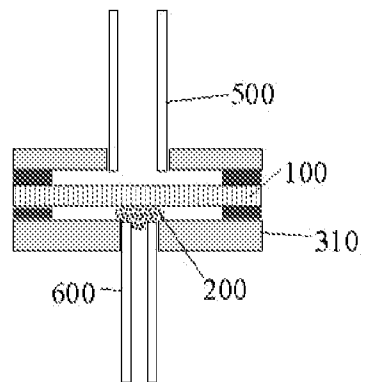


FIG. 9

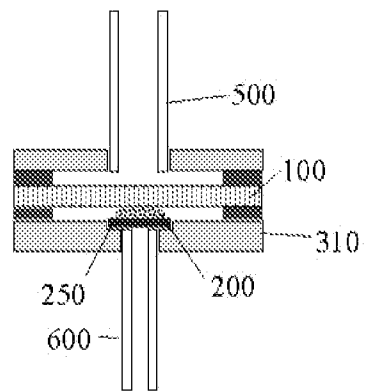


FIG. 10

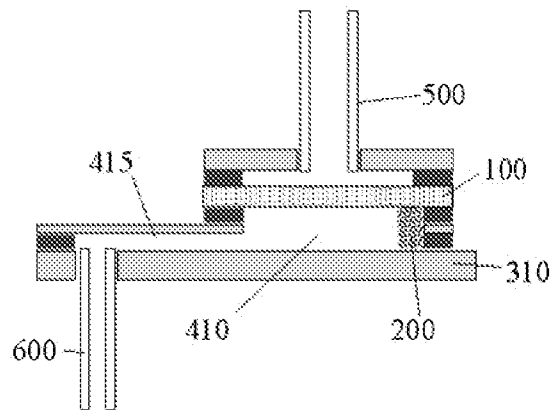


FIG. 11

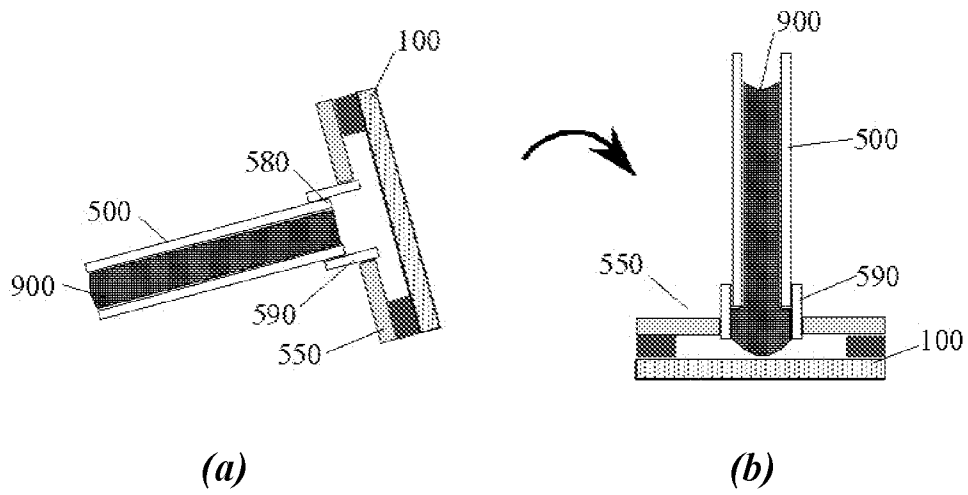


FIG. 12a & b

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/042865

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - B01D 61/00; B01D 61/14; B01D 63/00; B01D 63/02; B01D 71/68; B01L 3/00 (2016.01)

CPC - B01D 61/14; B01L 3/5023; B01L 3/502738; B01L 2200/026 (2016.08)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - B01D 61/00, B01D 61/14, B01D 63/00, B01D 63/02, B01D 71/68, B01L 3/00, F16K 99/00, G01N 1/28, G01N 33/49 (2016.01)
CPC - B01D 61/14, B01L 3/5023, B01L 3/502738, B01L 2200/026, B01L 2200/0605, B01L 2300/0681, B01L 2300/069, B01L 2300/0816 (2016.08)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

IPC(8) - B01D 61/00, B01D 61/14, B01D 63/00, B01D 63/02, B01D 71/68, B01L 3/00, F16K 99/00, G01N 1/28, G01N 33/49; CPC - see above (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Orbit, Google Scholar, Google

Search terms used: automatic, plasma, separation, metering, mcneely, international point of care, primecare, blood separation, membrane, plasma membrane, soluble matrix, dissolves, filtrate, metered, transport, blood, collect, plasma separation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2015/044454 A2 (STEMME et al) 02 April 2015 (02.04.2015) entire document	1-15
Y	US 2013/0175213 A1 (DORRER et al) 11 July 2013 (11.07.2013) entire document	1-13
Y	WO 2012/015926 A2 (NORTHWESTERN UNIVERSITY) 02 February 2012 (02.02.2012) entire document	7
Y	US 2006/0011545 A1 (LATZA) 19 January 2006 (19.01.2006) entire document	14, 15
P, A	WO 2015/191406 A1 (MCNEELY) 17 December 2015 (17.12.2015) entire document	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search

15 September 2016

Date of mailing of the international search report

04 OCT 2016

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