ON-LINE DRUG DELIVERY SYSTEM IN EXTRACORPOREAL THERAPY

Background Of The Invention

This invention relates to the field of extracorporeal treatment of fluids and particularly blood, where drugs or other biological solutions, such as monoclonal antibody solutions, need to be added at precisely controlled rates, including at rates responsive to other information and/or conditions throughout the extracorporeal treatment circuit. More particularly, it relates to the treatment of cells with photoactivatable compounds and radiation and specifically, to clinically useful systems for the extracorporeal treatment of blood cells, especially leukocytes, with UV radiation.

It is well-known that a number of human disease states may be characterized by the overproduction of certain types of leukocytes, including lymphocytes, in comparison to other populations of cells which normally comprise whole blood. Excessive or abnormal lymphocyte populations result in numerous adverse effects to patients including the functional impairment of bodily organs, leukocyte mediated autoimmune diseases and leukemia related disorders many of which often ultimately result in fatality.

For best results in extracorporeal chemotherapy, it is necessary to deliver drug molecules to a target location in the blood at a desired drug concentration. For instance, in current extracorporeal photochemotherapy (photopheresis) the patient takes crystalline 8-methoxypsoralen ("8-MOP") capsules orally. Two (2) hours later, when the 8-MOP concentration in patient's blood is at maximum level, the peripheral blood is drawn from the patient, anticoagulated, and pumped into a rotating

centrifuge bowl where it is separated into three layers; plasma, buffy coat, and packed red blood cell layers. The plasma and buffy coat layers are separated from the bowl. See, for example, U.S. Pat. No. 4,568,328 to King, U.S. Patent No. 4,573,960 to Goss, and U.S. Patent No. 4,623,328 to Hartranft.

The collected buffy coat is mixed with plasma and normal saline and recirculated through a photoactivation chamber (photoceptor) where the blood cells in the circulating solution are exposed to the UVA irradiation in the presence of the photoactivatable drug, 8-MOP molecules. The treated cells are immediately returned to the patient. In this therapy the drug concentration in the patient blood is one of the most important parameters.

Inter- and intra-patient variation in bioavailability of 8-MOP is extremely high, however, and in certain individuals, such as uremic patients, the bioavailability of 8 MOP is near zero. It is therefore, very difficult to deliver consistent and optimum therapy to patients.

Several methods are currently used to deliver drugs in liquid form into an extracorporeal circuit, but, none of them can achieve the goal satisfactorily.

Among the more common methods currently in use is to inject a precalculated amount of liquid drug into a part of an extracorporeal blood circuit, such as a drip chamber or blood bag, and hand-mix it. Another common approach is to drip the drug into the drip chamber. These methods are not very precise, thereby making it difficult to control the concentration of the drugs during the extracorporeal therapy process.

Another method currently in use imparts a drug solution into the blood circuit by means of a syringe pump. In this method the drug injection rate can be precisely controlled, but is independent of the blood flow rate. Thus, the drug concentration in the blood circuit or reaction chamber varies as the blood flow rate in the extracorporeal circuit changes.

Still another commonly used method uses a peristaltic drug delivery pump, such as heparin pump, which is slaved to the blood pump rate. This method has limited applications for several reasons. First, the blood supply from the patient peripheral circuit to the extracorporeal circuit should remain substantially constant throughout the treatment. However, if the blood supply changes, which happens frequently during the treatment due to the movement of needle or other reasons, a negative pressure can develop within the extracorporeal circuit, endangering the patient. For this reason, most dialysis patients need to have a fistula implanted as a blood access. This method also requires the use of an elastic pump chamber tubing, such as silicone or PVC, which in many instances adsorbs drug molecules.

In the method mentioned above, no attempt is made to achieve a good mixing of the delivered drug with the blood. Mixing is left to the natural behavior of the fluid flow. Because the flow is laminar in most of the extracorporeal blood circuit, any liquid drug stream injected into the blood stream requires a substantial amount of time or flowing distance to achieve good mixing.

Known methods for extracorporeal therapy hold the buffy coat portion of the patient's blood throughout all the treatment cycles of a therapy session, and therefore do not return any portion of the patient's buffy coat to

the patient until the conclusion of the treatment session. In order to minimize the time during which a patient is without buffy coat, it is desirable to have an extracorporeal treatment system which returns whole blood (including buffy coat) to the patient at the end of each treatment cycle in the therapy session.

It is therefore an object of the present invention to overcome the foregoing drawbacks by providing systems and methods for increasing the effectiveness of extracorporeal treatment and for increasing patient safety thereby also raising patient comfort level as well as meeting acceptable regulatory standards.

It is another related object to provide suitably automated systems and methods which can be monitored and operated by less trained personnel thereby lowering treatment costs in accordance with recently enacted fiscal policies.

It is still another related object to provide methods and systems for use in the extracorporeal treatment of patients wherein drug concentration is regulated and delivered to a reaction chamber, such as used in extracorporeal chemotherapy, to maximize the effectiveness of such therapy.

It is still another related object to provide an extracorporeal treatment system which returns whole blood to the patient at the end of each treatment cycle in the therapy session.

It is still another related object to provide an extracorporeal treatment system which achieves a complete and uniform mixing of a delivered drug with blood flowing in an extracorporeal circuit.

It is still another related object to provide an extracorporeal treatment system which is able to detect blood loss in the extracorporeal circuit.

It is still another related object to provide an extracorporeal treatment system which is able to detect the presence of air in the extracorporeal circuit.

It is still another related object to provide an extracorporeal treatment system which includes a syringe pump and a pressure pillow sensor which prevents a drug in the syringe from being drawn into the blood circuit when there is negative pressure in the blood line.

These and still other objects of the invention will become apparent upon study of the accompanying drawings and description of the invention.

Brief Description Of The Drawings

Fig. 1 is a block diagram illustrating an on-line extracorporeal drug treatment system operating in accordance with a preferred embodiment of the present invention.

Fig. 2 is a flow diagram illustrating the operation of the system of Fig. 1 in accordance with a preferred embodiment of the present invention.

Fig. 2A is a flow diagram illustrating the operation of the system of Fig. 1 in accordance with a further preferred embodiment of the present invention.

Fig. 3 is a flow diagram illustrating the operation of blood and syringe pumps in accordance with a preferred embodiment of the present invention.

Figs. 4 and 4A are a flow diagram illustrating the operation of a system for controlling the irradiation time of blood contained in a centrifuge treatment chamber in accordance with a preferred embodiment of the present invention.

Fig. 5 is a block diagram of a system for detecting air in the blood circuit of an extracorporeal blood treatment system in accordance with a preferred embodiment of the present invention.

Fig. 6 is a side view of a drug mixer for mixing a drug solution with a patient's blood within an extracorporeal blood circuit in accordance with a preferred embodiment of the present invention.

Fig. 7 is a block diagram of a system for detecting blood loss from the blood circuit of an extracorporeal blood treatment system in accordance with a preferred embodiment of the present invention.

Fig. 8 is a circuit diagram of a system for monitoring the state of irradiation lamps positioned within a centrifuge chamber in accordance with a preferred embodiment of the present invention.

Figs. 9 and 9A are front views of a syringe pump according to a preferred embodiment of the present invention.

Summary Of The Invention

The present invention is directed to a method and apparatus for extracorporeally treating a patient's blood on-line. Whole blood is initially collected from the patient and mixed with a medicinal solution to form a

whole-blood medicinal solution mixture. A quantity of treated whole blood if formed by providing the whole-blood medicinal solution mixture to a centrifuge chamber and exposing the whole-blood medicinal solution to radiation. The quantity of treated whole blood is then emptied from the centrifuge chamber, stored in a return storage medium, and re-infused into the patient. The process is successively repeated from the initial collection stage for a plurality of cycles. In a preferred embodiment, the treatment process is expedited after the first volume of whole blood has been treated by simultaneously collecting whole blood from the patient while at the same time treating the volume of whole blood that was collected from the patient in the previous cycle.

In accordance with another aspect of the present invention, a continuous flow of blood collected from a patient is provided into a rotating centrifuge chamber. As the flow of blood collected from the patient is being received by the rotating centrifuge chamber, the blood currently contained in the rotating centrifuge chamber is irradiated with light. As the blood is being irradiated in the rotating centrifuge chamber, changes in the volume of blood contained in the rotating centrifuge chamber and the cumulative light energy applied to the blood in the chamber are monitored over time. A remaining irradiation time value is determined in accordance with changes in the volume of blood currently contained in the rotating centrifuge chamber and the cumulative light energy value. A determination is made whether the irradiating step is finished by comparing the remaining irradiation time value to a predetermined constant. If the comparison of the remaining irradiation time value with the predetermined constant does not indicate that the irradiating step is finished, then new remaining irradiation time values are successively determined until a comparison of the

remaining irradiation time value with the predetermined constant indicates that the irradiating step is finished.

In accordance with a further aspect of the present invention, an on-line system and method for extracorporeally delivering a predetermined concentration of a medicinal solution into a patient's blood are provided. Initially, blood is extracted from the patient and provided to a blood reservoir. The extracted blood is then pumped from the blood reservoir into a blood line at a first pumping rate. The level of blood in the reservoir is sensed based on the extracted blood currently remaining in the blood reservoir to determine a sensed blood reservoir level. The first pumping rate is adjusted in response to the sensed blood reservoir level. A medicinal solution is pumped into the blood line at a second pumping rate which is adjusting in response to the first pumping rate. The extracted blood in the blood line is mixed with the medicinal solution in the blood line, and later returned to the patient.

In accordance with a still further aspect of the present invention, an improved syringe pump for use in an on-line system for extracorporeally delivering a predetermined concentration of a medicinal solution into a patient's blood is provided. The syringe pump includes a mounting block for rigidly receiving a body portion of a syringe, the syringe being filled with a medicinal solution and being coupled to a blood path in the on-line system. A push block is slidably secured to the mounting block, the push block having a plunger clip opening for securing a top end of a plunger portion of the syringe to the push block. Driving means, coupled to the mounting block and the push block, are provided for driving the push block toward the mounting block in response to a control signal. The plunger clip opening in the push

block is shaped so as to prevent the on-line system from drawing medicinal solution from the syringe when there is negative pressure in the blood path.

In accordance with yet a still further aspect of the present invention, a blood loss detector is provided for use in connection with an on-line system for extracorporeally treating a patient's blood that includes a reaction chamber for processing the patient's blood, the reaction chamber having a drain line for removing blood from the on-line system. A first conductive tube having a first end coupled to the drain line is provided. An insulator block having a first channel for receiving a second end of the first conductive tube is also provided. The insulator block further includes a second channel for receiving a first end of a second conductive tube. The first and second channels are connected in the insulator block by a hollow fluid bridge for carrying fluid from the second end of the first conductive tube to the first end of the second conductive tube. Sensing means are provided for signaling the presence of an electrical connection between the first and second conductive tubes when a patient's blood flows through the fluid bridge, thereby indicating a blood loss from the extracorporeal circuit.

In accordance with a still further aspect of the present invention, an air detector is provided for use in connection with an on-line system for extracorporeally treating a patient's blood. First and second oscillators are positioned on opposing sides of a blood transmission line for transporting the patient's blood through the on-line system. A signal transmitter is coupled to the first oscillator, and a signal receiver is coupled to the second oscillator. A microprocessor is coupled to the signal transmitter and the signal receiver. The microprocessor includes comparing means for comparing signals transmitted

by the signal transmitter to signals received by the signal receiver. The microprocessor further includes air detection means, responsive to the comparing means, for signalling the presence of air in the blood transmission line.

In accordance with a still further aspect of the present invention, an improved method and apparatus for mixing first and second fluids moving in a combined laminar flow within a single fluid transmission line are provided. The combined laminar flow is directed into a fluid mixer through a mixer input port. The combined laminar flow is then passed through a mesh material positioned inside the fluid mixer, thereby forming a mixture of the first and second fluids.

Detailed Description Of The Preferred Embodiment

Referring now to Fig. 1, there is shown a block diagram of an on-line extracorporeal drug treatment system 100 operating in accordance with a preferred embodiment of the present invention. System 100 operates in several modes which are performed in a repetitive fashion for a plurality of cycles during a treatment session. In the collection mode, system 100 collects whole blood from patient 10, adds a precisely controlled amount of medicinal solution to the whole-blood via syringe pump 50, and provides the whole blood medicinal solution mixture to reaction chamber 85 for treatment. After the blood in reaction chamber 85 has been treated, system 100 switches to a return mode, during which treated whole blood is pumped by blood pump 80 to return bag 60. When the contents of reaction chamber 85 have been pumped into return bag 60, system 100 switches to a re-infusion mode during which treated whole blood from return bag 60 is returned to patient 10 through gravity pressure.

In a first preferred embodiment (shown in Fig. 2), system 100 successively cycles through its three modes ten times during a treatment session. In each such cycle, as little as 150 ml of whole blood may be collected, treated and returned (or re-infused) into patient 10. In alternate embodiments of the system shown in Fig. 2, an operator may vary both the number of treatment cycles and the volume of whole blood that is treated in each cycle. As shown in Fig. 2, system 100 is preferably primed with a saline solution prior to initiation of the treatment session.

In a second preferred embodiment (shown in Fig. 2A), system 100 repeats its three modes ten times during a treatment session. However, in contrast to the system of Fig. 2, in this embodiment the treatment process is expedited after the first volume of whole blood has been collected, treated and emptied into the return bag 60. In the system of Fig. 2A, after the first volume of whole blood has been collected, treated and emptied into the return bag 60, a second volume of blood is collected from the patient 10, mixed with a medicinal solution and provided to reaction chamber 85. Thereafter, the second volume of blood then in reaction chamber 85 is treated while at the same time the blood in return bag 60 (from the previous treatment cycle) is simultaneously re-infused into patient 10. It was found that the overall treatment time for a patient could be reduced by performing the treatment and re-infusion steps simultaneously. In addition, it was found that blood line 12 was less prone to clogging when the treatment and re-infusion steps were performed simultaneously because this reduced the amount of time that blood line 12 was stagnant or inactive. As was the case with the system of Fig. 2, in the system of Fig. 2 as little as 150 ml of whole blood may be collected, treated and re-infused into patient 10 in each

treatment cycle. In alternate embodiments, however, an operator may vary both the number of treatment cycles and the volume of whole blood that is treated in each cycle.

As discussed more fully below, the flow of blood throughout system 100 is precisely controlled throughout the treatment session by microprocessor controller 45 which controls both the flow rate and direction of blood in the extracorporeal circuit. Among other devices, microprocessor controller 45 is coupled both to blood pump 80 and syringe pump 50, as well as to solenoid activated pinch clamps 65, 70, 75. During the collection mode of system 100, blood pump 80 pumps whole blood from pressure pillow reservoir 35 into reaction chamber 85. As the whole blood exits pressure pillow reservoir 35, syringe pump 50 injects a medicinal solution into the blood circuit at a controlled rate. In the collection mode, microprocessor controller 45 controls the flow direction of whole blood in the extracorporeal circuit by placing clamps 65, 70 in a closed state, while placing clamp 75 in an open state.

During the return mode of system 100, the direction of blood pump 80 is reversed, and blood pump 80 pumps treated whole blood from reaction chamber 85 to return bag 60. In the return mode, microprocessor controller 45 controls the direction of treated blood in the extracorporeal circuit by opening clamp 70, while maintaining clamps 65, 75 in a closed position. Finally, during the re-infusion mode, treated blood from the return bag 60 flows by gravity first to pressure pillow reservoir 35, and then back into the patient. In the preferred embodiment, the same needle that was used to collect blood from patient 10 in the collection mode is used to re-infuse the treated blood into the patient. In the re-infusion mode, microprocessor controller 45 controls the

flow of blood in the extracorporeal circuit by opening clamp 65, while maintaining clamps 70, 75 in a closed position.

Against this overview of the operation of the present invention, the details of system 100 will be described more fully below. Referring again to Fig. 1, during the collection mode, whole blood is extracted from patient 10 through a needle and provided to system 100 through disposable blood tubing 12. The patient's blood preferably flows by gravity into pressure pillow reservoir 35. Prior to reaching pressure pillow reservoir 35, the patient's blood is anticoagulated by anticoagulation pump 15, which provides heparin from bag 20 to the patient's blood. The whole blood in pressure pillow reservoir 35 is pumped into reaction chamber 85 by blood pump 80 at a rate controlled by microprocessor controller 45. During the collection mode, pressure pillow sensor 40 continuously senses the level of blood in reservoir 35 and sends a signal representative of the reservoir level to microprocessor controller 45. If the blood level in reservoir 35 falls below a predetermined minimum threshold, the pump speed of pump 80 is reduced to zero until such time as the blood level in reservoir 35 exceeds the predetermined minimum level. The purpose behind reducing the speed of pump 80 when the level of blood in reservoir 35 is low, is to insure that the blood flow out of patient 10 is entirely gravity driven and that blood is never pumped out of the patient by blood pump 80. The pillow sensor 40 could be made from many different types of sensors such as electromechanical, optical, ultrasonic, or piezoelectric sensors. In addition, in an alternate embodiment, the pump speed of pump 80 could be ramped down gradually as the blood level in the pressure pillow reservoir decreases.

As pump 80 pumps whole blood from pressure pillow reservoir 35 to reaction chamber 85 during the collection mode, a liquid drug is pumped into the blood circuit from syringe pump 50 at a rate controlled by microprocessor controller 45. In calculating the syringe pump rate, microprocessor controller 45 in effect slaves the pumping rate of syringe pump 50 to the pumping rate of blood pump 80 such that, syringe pump 50 injects drug solution into the blood circuit only when blood pump 80 is in an ON state. In addition, as described more fully below in conjunction with Fig. 3, syringe pump 50 operates at an increased pumping rate during the first cycle of a treatment session in order to compensate for drug absorption by the tubing and other materials forming system 100.

Following the injection by syringe pump 50 of the drug solution into the extracorporeal circuit, the blood stream, combined with the delivered liquid drug, flows into specially designed drug mixer 55 where the two relatively unmixed streams (i.e., the whole blood stream and the drug solution stream) are broken up and mixed to form a whole blood drug solution mixture which is pumped by pump 80 into reaction chamber 85. Further details of drug mixer 55 are set forth below in conjunction with the description of Fig. 6.

In a preferred embodiment of the present invention, a photoactivatable agent, such as a psoralen, and still further preferably 8-methoxypsoralen, in liquid form is injected in the blood circuit by syringe pump 50 during the collection mode of system 100, although other drug or biological solutions, such as monoclonal antibody solutions or other photoactivatable agents may also be used. Also in a preferred embodiment, reaction chamber 85 constitutes a rotatable centrifuge that includes within

its interior a photoactivation system for irradiating the whole blood drug solution mixture with UV light while the centrifuge is rotating. A preferred reaction chamber 85 which includes a photoactivation system within its interior is illustrated and operates substantially as shown and described in U.S. Pat. No. 4,921,473, which patent disclosure is incorporated herein by reference.

Although in the preferred embodiment of system 100, whole-blood from a patient 10 is collected and provided to the system for treatment and then re-infused into the patient, it will be understood by those skilled in the art that blood provided from other sources, such as for example, a donor center (not shown) may be provided to system 100 for treatment. Where blood collected from a donor center is provided to system 100 for treatment, the treated blood may either be directly infused into a patient by system 100 or collected in a container (not shown) and infused into a patient at a later time. In addition, although in the preferred embodiment, system 100 operates to treat whole-blood, it will be understood by those skilled in the art that blood formed from fractional components of whole-blood may also be treated by system 100.

Referring now to Fig. 3, there is shown a flow diagram illustrating a system 300 for operating blood pump 80 and syringe pump 50 in accordance with a preferred embodiment of the present invention. When system 100 is operating in its collection mode, the operation rate of blood pump 80 is set in such a way that the pumping rate is less than the blood flow from patient 10 to pressure pillow reservoir 35. Consequently, during normal operation, pressure pillow reservoir 35 should remain fully filled with the patient blood. However, if the blood flow from the patient to pressure pillow reservoir

35 slows down for any reason, the blood volume inside pressure pillow reservoir 35 may decrease eventually causing pressure pillow reservoir 35 to collapse. This undesirable situation is prevented by the pillow sensor 40 which detects the level of the blood in pressure pillow reservoir 35 and signals this condition to microprocessor controller 45. If the blood level in pressure pillow reservoir 35 decreases, microprocessor control system 45 slows down the blood pump rates of pumps 50 and 80. This feedback mechanism helps patient 10 receive uninterrupted and safer treatment.

The operation of the feedback system described generally in the paragraph immediately above is illustrated in more detail as feedback system 300 in Fig. 3. Referring still to Fig. 3, system 300 begins at step 310 by monitoring pressure pillow sensor 40 to determine the level of blood in reservoir 35. A control signal representative of the level of blood in the reservoir is then provided to microprocessor controller 45 by sensor 40. In step 320, microprocessor controller 45 determines, in response to the control signal received from sensor 40, whether the level of blood in pressure pillow reservoir 35 has fallen below a predetermined level, thereby indicating that pressure pillow reservoir 35 has collapsed. If a determination is made that pressure pillow reservoir 35 has collapsed, then processing proceeds to step 330, wherein microprocessor 45 sends control signals to pumps 50 and 80 setting both pumps to an OFF state. Alternatively, if a determination is made at step 320 that pressure pillow reservoir 35 has not collapsed, then processing proceeds to step 340, wherein microprocessor 45 sends a control signal to pump 80 setting that pump to an ON state.

Next, in step 350, microprocessor controller 45 determines whether system 100 is operating in the first cycle of a treatment session. If system 100 is in the first cycle of the treatment session, microprocessor controller 45 sends a control signal to syringe pump 50 turning that pump to an ON state and setting its pumping rate at a first rate (R1). Alternatively, if system 100 is not in the first cycle of the treatment session, microprocessor controller 45 sends a control signal to syringe pump 50 turning that pump to an ON state and setting its pumping rate at a second rate (R2) which is less than (R1). In the preferred embodiment, an increased pumping rate (R1) is used in the first cycle to compensate for the drug adsorption rate of the tubing and other materials that form system 100. After the pumping rate of syringe pump 50 is set, processing continues with step 380, wherein microprocessor controller 45 determines whether the volume of whole blood to be treated in the current cycle has been provided to reaction chamber 85 by pump 80. Microprocessor controller 45 determines whether the cycle volume has been reached by repeatedly monitoring the state and pumping rate of blood pump 80 during the collection mode. If the cycle volume has not been reached, system 300 returns to step 310 and the process described above is repeated; otherwise, processing passes to step 390. In step 390, microprocessor controller 45 sends control signals to pumps 50 and 80 setting both pumps to an OFF state.

Referring now to Figs. 4, 4A, there is shown a flow diagram illustrating the operation of an irradiation time control system 400 for controlling the irradiation time of blood contained in reaction chamber 85 during the treatment mode of system 100 in accordance with a preferred embodiment of the present invention. During the treatment mode, a continuous flow of blood collected from

patient 10 is mixed with a medicinal solution and provided to reaction chamber 85 by blood pump 80. As mentioned above, in the preferred embodiment, reaction chamber 85 is a centrifuge which includes an interior photoactivation system for irradiating the patient's blood with UV light. In the present invention, system 100 does not wait until the entire cycle volume of blood (described in connection with step 350 above) is received into the centrifuge chamber before beginning to irradiate the patient's blood with UV light. Instead, on a continuous basis as blood is received into chamber 85 during the treatment mode, the blood is separated into its constituent parts by the rotating centrifuge and then irradiated by the UV lights positioned inside the centrifuge chamber. By separating and irradiating the patient's blood on a continuous basis during the collection mode, the present invention minimizes the treatment time for patient 10.

The operation of the irradiation time control system described generally in the paragraph immediately above is illustrated in detail as system 400 in Fig. 4. Referring still to Fig. 4, system 400 begins at the beginning of the treatment mode in step 405 by initializing a remaining irradiation time value (T_I) to a seed value (T_s). The remaining irradiation time value is a running value which is repeatedly incremented and decremented, and which represents the remaining time (in seconds) during which the blood in chamber 85 is to be subjected to UV light before such blood is returned and re-infused into the patient. The seed value (T_s) is set to compensate for the fact that UV light from the photoactivation system cannot penetrate whole blood, but instead such light can only penetrate through a buffy coat layer. Since it takes whole blood approximately 2-3 minutes after it has been received into a rotating centrifuge to separate into its constituent parts, any UV applied to the blood during this

initial 2-3 minutes is useless for purposes of treating the blood. Therefore, in the preferred embodiment, T_s is preferably set between 120-180 seconds. In initialization step 405, a time marker T_{prev} is set to zero, and a volume marker V_{prev} is set to zero. By setting T_{prev} and V_{prev} to zero, initialization step 405 signifies that the irradiation step begins at time zero with chamber 85 in an empty state.

After initialization step 405, a determination is made in step 410 regarding the current volume of blood (V_{curr}) in chamber 85. Since blood is continuously being pumping into chamber 85 during at least part of the treatment mode, the value of V_{curr} will vary with time. Microprocessor controller 45 determines V_{curr} by monitoring the state and speed of pump 80 throughout each treatment cycle. In step 415, a change in blood volume (deltaV) is determined by differencing V_{curr} and V_{prev}, and in step 420 V_{prev} is replaced with V_{curr}. In step 425, the time that has elapsed since initiation of the irradiating step (T_{curr}) is saved. In step 430, a change in elapsed time (deltaT) is determined by differencing T_{curr} and T_{prev}, and in step 435 T_{prev} is replaced with T_{curr}. In step 440, a cumulative light energy value (UV_{cum}) representing the total light energy provided to the blood in chamber 85 during the treatment cycle is calculated. In order to determine this cumulative light energy value, microprocessor controller 45 monitors the state (ON/OFF) of the UV lamps in chamber 85 during the treatment cycle. In addition, microprocessor controller 45 maintains a running record of the age (in hours used) of each bulb in chamber 85 and adjusts the cumulative light energy value for the fact that the light energy emitted by each bulb decreases as the bulb is used.

Although in Fig. 4, the steps for determining deltaV (steps 410, 415, 420), deltaT (steps 425, 430, 435) and UV_{cum} (step 440) are shown in parallel, these values may also be determined sequentially. In the preferred embodiment of system 400, deltaV is determined 40 times per second, while deltaT and UV_{cum} are determined 5 times per second. Frequent calculations of these values are important to insure that the transition of T_I to zero is caught immediately.

In step 445, following calculation of deltaV, deltaT and UV_{cum}, V_{curr} is compared to a threshold (V_{thresh}) which represents the threshold volume of blood that activates the deltaV and deltaT terms during the calculation of T_I in step 485 (described below). If V_{curr} is greater than or equal to V_{thresh}, then in step 450 first (A) and second (B) irradiation time calculation constants are set to one. If V_{curr} is not greater than or equal to V_{thresh}, then in step 455 UV_{cum} is compared to a threshold (UV_{thresh}). If UV_{cum} is greater than or equal to UV_{thresh}, then in step 460 the first and second irradiation time calculation constants A and B are set to zero and one, respectively; otherwise, in step 465, the first and second irradiation time calculation constants A and B are both set to zero. A preferred value for UV_{thresh} is 300. In step 470, system 400 determines (or confirms) whether the UV lights in chamber 85 are in fact in an ON state. A preferred circuit for determining the state of the UV lights in chamber 85 is described below in conjunction with Fig. 8. If step 470 determines that the UV lights are in fact in an ON state, then a third irradiation time calculation constant (U) is set to one in step 475; otherwise the third irradiation time calculation constant (U) is set to zero.

Following the determination of the three irradiation time calculation constants, microprocessor controller 45

updates the value of T_I in accordance with equation (1) below:

$$T_I = T_I + (A * C * deltaV) - (B * U * deltaT) \quad (1)$$

where, C is a constant representing the number of seconds of irradiation time to be added to the remaining irradiation time T_I as each milliliter of blood is added into chamber 85. In step 490, T_I is compared against a zero threshold. If T_I is not greater than zero, this indicates that the irradiation step is finished; otherwise, the process is repeated as shown in Fig. 4 until T_I reaches or falls below the zero threshold.

Referring again to Fig. 1, the preferred embodiment of system 100 includes a plurality of air detectors 25, 30 for detecting the presence of air in the extracorporeal circuit. In the preferred embodiment, if air is detected in system 100, an alarm is generated immediately informing an operator that air has been detected. Referring now to Fig. 5, there is shown a block diagram of an air detector 25, 30. First and second oscillators 505, 510 are positioned on opposing sides of blood transmission line 12 for transporting the patient's blood through the on-line system. First and second crystal oscillators 505, 510 are held in place by air detector mounting block 515 which has recesses that are adapted to receive oscillators 505, 510. A signal transmitter 520 is electrically coupled to first oscillator 505, and signal receiver 525 is electrically coupled to second oscillator 510. Microprocessor controller 45 is coupled to signal transmitter 520 and signal receiver 525. Microprocessor controller 45 includes comparing means for periodically comparing signals transmitted by signal transmitter 520 to signals received by signal receiver 525. Since transmitter 520 repeatedly broadcasts the same signal,

unexpected changes in the signal received by receiver 525 indicate the presence of air in tube 12. Microprocessor controller 45 includes air detection means, responsive to the comparing means, for signalling the presence of air in the blood transmission line when there is an unexpected change in the signal received by receiver 525.

In the preferred embodiment of the present invention, the operation of each air detector 25, 30 is periodically tested to verify that it is functioning properly. In particular, on a periodic basis, signal transmitter 520 is turned off and any signal received by receiver 525 is monitored by microprocessor controller 45. If, during this verification test, an unexpected signal is received by receiver 525, this condition would indicate that the air detector is not operating properly either because the output of transmitter 520 is stuck or for some other reason. In the preferred embodiment, if microprocessor controller 45 determines that an air detector is not functioning properly, an alarm is sounded signalling the state of the system to an operator.

Although in Fig. 1, air detectors 25, 30 are positioned adjacent to anticoagulation pump 15 and mixer 55, respectively, it will be understood by those skilled in the art that air detectors 25, 30 may be positioned throughout system 100. It will also be understood by those skilled in the art that air detectors 25, 30 may be used to sense the presence of air in fluid circuits other than extracorporeal blood circuits.

Referring now to Fig. 6, there is shown a side view of drug mixer 55 for mixing a drug solution with a patient's blood within an extracorporeal blood circuit in accordance with a preferred embodiment of the present invention. Mixer 55 is formed of a sealed hollow chamber

610 with an opening 600 for receiving unmixed fluids and an opening 650 for outputting mixed fluids. The interior of chamber 610 is divided into compartments 620 and 630 by a mesh bag 640 which is secured in a circular manner along its opening 660 to the interior of hollow chamber 610. During operation of fluid mixer 55, first and second fluids moving in a combined laminar flow within a single fluid transmission line are provided to mixer 55 through input port 600. The combined laminar flow is then passed through mesh bag 640 positioned inside the fluid mixer, thereby forming a mixture of the first and second fluids. Mesh bag 640 achieves an efficient mixing of the first and second fluids by disrupting the combined laminar flow of these fluids. When mixer 55 is used to mix blood with other solutions, mesh 640 preferably has a hole size between 100 and 600 microns. It will be understood by those skilled in the art that mixer 55 may be used to mix fluids other than blood, and may be used in applications other than extracorporeal blood circuits.

In the preferred embodiment of the present invention, system 100 includes means for detecting blood loss from the extracorporeal circuit. Such blood loss could occur, for example, if a hole or crack develops in the centrifuge treatment chamber, or if an overflow condition were to develop inside the centrifuge chamber. When system 100 detects that blood is being lost from the extracorporeal circuit, an alarm is triggered signalling this event to an operator. Referring now to Fig. 7, there is shown a block diagram of a preferred system 700 for detecting blood loss from system 100 in accordance with a preferred embodiment of the present invention. In the preferred embodiment, reaction chamber 85 includes an outer housing (not shown) for catching any leakage or overflow from the reaction chamber. The lower-most portion of this outer housing is connected to a drain line 710 for carrying away any blood

that leaks or spills into the outer housing. In system 700, a first electrically conductive tube 720 having a first end coupled to drain line 710 is provided. An insulator block 730 having a first hollow channel 735 for receiving a second end of first conductive tube 710 is also provided. Insulator block 730 is not electrically conductive. Insulator block 730 further includes a second hollow channel 740 for receiving a first end of a second conductive tube 750. First and second hollow channels 735, 740 are connected in insulator block 730 by a hollow fluid bridge 755 for carrying fluid from the second end of first conductive tube 720 to the first end of second electrically conductive tube 750. A comparator circuit 760 is provided for sensing the presence of an electrical connection between first and second conductive tubes 720, 750. Since the conductivity of blood flowing through hollow fluid bridge 755 is sufficient to form an electrical connection between the first and second conductive tubes 720, 750, comparator circuit 760 will sense an electrical connection between the conductive tubes whenever blood flows through hollow fluid bridge 755, thereby signalling a blood loss from the extracorporeal circuit. The output of comparator circuit 760 is coupled to a latching relay circuit 770 that causes a shutdown of blood pump 80 and the sounding of an audible alarm whenever an electrical connection is sensed between first and second conductive tubes 720, 750.

As discussed above in connection with Fig. 4, in step 470 of system 400, the present invention repeatedly monitors the state (ON/OFF) of the UV irradiation lamps inside reaction chamber 85. Referring now to Fig. 8, there is shown a circuit diagram of a preferred system 800 for monitoring the state of an irradiation lamp 810 positioned within a centrifuge chamber in accordance with a preferred embodiment of the present invention. In

system 800, a sine wave generator 820 and a resistor 830 are placed in series with irradiation lamp 810. When lamp 810 is in an ON state, a voltage is generated across resistor 830, thereby causing a logic 0 signal at the output of circuit 840. Alternatively, when lamp 810 is in an OFF state, no voltage is generated across resistor 830 and the output of circuitry 840 will be a logic 1 signal. In the preferred embodiment of the present invention, three separate irradiation lamps are positioned within chamber 85, and a separate system 800 is coupled to each of these lamps so that the state of each lamp may be separately monitored during the treatment process.

Finally, referring now to Figs. 9, 9A, there are shown front views of a preferred embodiment of syringe pump 50 according to the present invention. Syringe pump 50 includes a mounting block 900 for rigidly receiving a body portion of a syringe 910. Syringe 910 is preferably a glass syringe and is filled with a medicinal solution. Syringe 910 is coupled (at syringe tip 920) to the extracorporeal blood circuit. A push block 930 is slidably secured to mounting block 900 by a pair of metal rods 940, 950 positioned on opposing sides of the plunger portion 960 of syringe 910. In the preferred embodiment, push block 930 includes a plunger clip opening 970 for securing the top end of plunger portion 960 to push block 930. The plunger clip opening 970 in push block 930 is shaped so as to prevent the on-line system from drawing medicinal solution from syringe 910 when there is negative pressure in the blood path connected to tip 920. Driving means (not shown, but positioned behind blocks 900, 930 in Figs. 9, 9A), coupled to mounting block 900 and push block 930, are provided for driving the push block 930 toward the mounting block 900 in response to a control signal provided by microprocessor controller 45. This control signal will communicate to the driving means whether

syringe pump 50 should be pumping at rate R1, rate R2 or whether pump 50 should be in an OFF state. In the preferred embodiment, the driving means used for driving push block 930 toward mounting block 900 is a worm drive mechanism. In the preferred embodiment of the present invention, syringe pump 50 includes a safety latch 980 that prevents system 100 from operating unless syringe 910 has been installed in mounting block 910. Fig. 9 shows safety latch 980 in its open state; and Fig. 9A shows safety latch 980 in its closed or locked state. A control signal prevents operation of the present invention whenever latch 980 is in an open state.

It will be understood by those skilled in the art that syringe pump 50 may be used to precisely deliver controlled quantities of fluids other than medicinal solutions and in environments other than extracorporeal blood circuits. In addition, it will also be understood by those skilled in the art that system 100 has applications in dynamic liquid mixing environments including any extracorporeal blood treatments where drug solution or any biological solutions, such as monoclonal antibody solutions, needs to be added into the blood or other circuit at precisely controlled rate and well mixed before going into a treatment chamber.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes of the invention. Accordingly, reference should be made to the appended claims, rather than the foregoing specification, as indicating the scope of the invention.

* C L M S *

What Is Claimed Is:

1. An on-line method for extracorporeally treating blood, comprising the steps of:

(A) collecting blood from a blood source;

(B) mixing said collected blood with a medicinal solution and thereby forming a blood-medicinal solution mixture;

(C) forming a quantity of treated blood by introducing said blood-medicinal solution mixture into a treatment chamber and exposing said blood-medicinal solution to radiation therein; and

(D) emptying said quantity of treated blood from said treatment chamber and storing said quantity of treated blood in a return storage container.

2. The method of claim 1, wherein said blood source is a patient, further comprising the step of:

(E) re-infusing said quantity of treated blood into said patient.

3. The method of claim 2, further comprising the step of:

(F) repeating steps (A)-(E) a plurality of times during a single treatment session of said patient.

4. The method of claim 3, wherein a single needle is used both to collect said blood from said patient in step (A) and to re-infuse said quantity of treated blood into said patient in step (E).

5. The method of claim 4, wherein said treatment chamber is a centrifuge chamber.

6. The method of claim 5, wherein said step of collecting blood from said patient further comprises the steps of:

(1) opening a patient clamp positioned along a blood transmission path between said patient and said centrifuge chamber;

(2) closing a return clamp positioned along said blood transmission path between said centrifuge chamber and said return storage container; and

(3) closing a re-infusion clamp positioned along said blood transmission path between said return storage container and said patient.

7. The method of claim 6, wherein said step of emptying said quantity of treated blood from said centrifuge chamber further comprises the steps of:

(1) closing said patient clamp positioned along said blood transmission path between said patient and said centrifuge chamber; and

(2) opening said return clamp positioned along said blood transmission path between said centrifuge chamber and said return storage container.

8. The method of claim 7, wherein said step of re-infusing said quantity of treated blood into said patient further comprises the steps of:

(1) closing said return clamp positioned along said blood transmission path between said centrifuge chamber and said return storage container; and

(2) closing said patient clamp positioned along said blood transmission path between said centrifuge chamber and said patient.

9. The method of claim 3, wherein a quantity of treated blood formed during a previous cycle is re-infused into said patient during step (C).

10. The method of claim 1, wherein said collected blood is whole blood.

11. The method of claim 1, wherein said collected blood represents a fractional component of whole blood.

12. An on-line method for extracorporeally treating blood, comprising the steps of:

(A) continuously providing a flow of blood collected from a patient into a rotating centrifuge chamber;

(B) irradiating blood currently contained in said rotating centrifuge chamber with light as said flow of blood collected from said patient is being received by said rotating centrifuge chamber;

(C) monitoring, during said irradiating step, a change in volume of blood contained in said rotating centrifuge chamber over a period of time;

(D) monitoring, during said irradiating step, a cumulative light energy value representing total light energy provided to blood in said rotating centrifuge chamber during said irradiating step;

(E) determining, during said irradiating step, a remaining irradiation time value in accordance with said change in volume of blood currently contained in said rotating centrifuge chamber and said cumulative light energy value;

(F) determining whether said irradiating step is finished by comparing said remaining irradiation time value to a predetermined constant;

(G) if said comparison of said remaining irradiation time value with said predetermined constant in step (F) does not indicate that said irradiating step is finished, then repeating steps (C)-(F) until said comparison of said remaining irradiation time value with said predetermined constant in step (F) does indicate that said irradiating step is finished; and

(H) returning said blood contained in said centrifuge to said patient after said irradiating step is finished.

13. The method of claim 12, further comprising the steps of initializing said remaining irradiation time value and a previous volume value prior to said irradiating step.

14. The method of claim 13, wherein step (C) comprises the steps of:

(1) determining a current volume of blood contained in said rotating centrifuge chamber at the end of said period of period of time;

(2) determining said change in blood volume by differencing said current volume and said previous volume value; and

(3) replacing said previous volume value with said current volume.

15. The method of claim 14, further comprising the step of monitoring, during said irradiation step, whether lights in said rotating centrifuge chamber are in an ON state.

16. The method of claim 15, wherein step (E) comprises the steps of:

(1) comparing said current volume to a predetermined volume threshold;

(2) comparing said cumulative light energy value to a predetermined light energy threshold;

(3) initializing first and second irradiation time constants to zero;

(4) if said current volume equals or exceeds said predetermined volume threshold

* C L M S *

then setting said first and second irradiation time constants to one

otherwise, if said cumulative light energy value equals or exceeds said predetermined light energy threshold then setting said second irradiation time constant to one; and

(5) adjusting said remaining irradiation time value in accordance with said change in blood volume, said first and second irradiation time constants, and said monitoring of said lights in said rotating centrifuge chamber.

17. An on-line method for extracorporeally delivering a predetermined concentration of a medicinal solution into a patient's blood, comprising the steps of:

(A) extracting blood from said patient and introducing said extracted blood into a blood reservoir;

(B) pumping said extracted blood from said blood reservoir into a blood line at a first pumping rate;

(C) sensing a blood reservoir level in response to said extracted blood remaining in said blood reservoir to determine a sensed blood reservoir level;

(D) adjusting said first pumping rate in response to said sensed blood reservoir level;

(E) pumping said medicinal solution into said blood line at a second pumping rate;

(F) adjusting said second pumping rate in response to said first pumping rate;

(G) mixing said extracted blood in said blood line with said medicinal solution in said blood line; and

(H) returning said extracted blood to said patient after said mixing step.

18. The method of claim 17, further comprising the step of delivering said extracted blood and said medicinal solution to a reaction chamber after said mixing step and before said extracted blood is returned to said patient.

19. The method of claim 17, further comprising the step of repeating step (A)-(H) for a plurality of treatment cycles, and wherein said second pumping rate is adjusted upward during a first treatment cycle to compensate for a drug adsorption rate associated with said blood line.

20. The method of claim 17, wherein said second pumping rate is slaved to said first pumping rate.

21. The method of claim 17, wherein said mixing step is achieved solely by simultaneous flowing of said extracted blood and said medicinal solution in said blood line.

22. The method of claim 18, wherein said reaction chamber is a photoactivation chamber.

23. The method of claim 22, wherein said medicinal solution contains a psoralen.

24. The method of claim 17, wherein a syringe pump is used to pump said medicinal solution into said bloodline in step (E).

25. In an on-line system for extracorporeally delivering a predetermined concentration of a medicinal solution into a patient's blood, a syringe pump comprising:

(A) a mounting block for rigidly receiving a body portion of a syringe, said syringe being filled with said medicinal solution and being coupled to a blood path in said on-line system;

(B) a push block slidably secured to said mounting block, said push block having a plunger clip opening for securing a top end of a plunger portion of said syringe to said push block;

(C) driving means, coupled to said mounting block and said push block, for driving said push block toward said mounting block in response to a control signal; and

wherein said plunger clip opening prevents said on-line system from drawing said medicinal solution from said syringe when there is negative pressure in said blood path.

26. The syringe pump of claim 25, further comprising first and second rods positioned on opposing sides of said syringe for slidably securing said push block to said mounting block.

27. The syringe pump of claim 25, further comprising a microprocessor controller for providing said control signal to said driving means.

28. The syringe pump of claim 25, wherein said driving means is formed from a worm drive.

29. The syringe pump of claim 25, further comprising a safety latch for preventing operation of said on-line system in the absence of said body portion of said syringe being positioned in said mounting block.

30. In an on-line system for extracorporeally treating a patient's blood, said system including a reaction chamber for processing said patient's blood, said reaction chamber having a drain line for removing blood from said on-line system, a blood loss detector comprising:

(A) first and second electrically conductive tubes, said first conductive tube having a first end coupled to said drain line;

(B) an insulator block having a first channel for receiving a second end of said first conductive tube, said insulator block having a second channel for receiving a first end of said second conductive tube, said first and second channels being connected in said insulator block by a fluid bridge for carrying fluid from said second end of said first conductive tube to said first end of said second conductive tube;

(C) sensing means for signaling the presence of an electrical connection between said first and second conductive tubes when said patient's blood flows through said fluid bridge.

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31. The blood loss detector of claim 30, wherein said sensing means comprises a comparator having first and second comparator inputs, said first comparator input being electrically connected to said first conductive tube, said second comparator input being electrically connected to said second conductive tube.

32. The blood loss detector of claim 31, wherein said first comparator input is coupled to a positive voltage source and said second comparator input is coupled to ground.

33. In an on-line system for extracorporeally treating a patient's blood, said system including a blood transmission line for transporting said patient's blood through said system, an air detector comprising:

(A) first and second oscillators positioned on opposing sides of said transmission line;

(B) a signal transmitter coupled to said first oscillator;

(C) a signal receiver coupled to said second oscillator;

(D) a microprocessor coupled to said signal transmitter and said signal receiver, said microprocessor including comparing means for comparing signals transmitted by said signal transmitter to signals received by said signal receiver, said microprocessor further including air detection means, responsive to said comparing means, for signalling the presence of air in said transmission line.

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34. The air detector of claim 33, said microprocessor further comprising verification means for periodically testing said signal transmitter and said signal receiver by periodically turning said signal transmitter off and monitoring signals received by said signal receiver.

35. The air detector of claim 33, wherein said first and second oscillators are crystal oscillators.

36. A method for mixing first and second fluids moving in a combined laminar flow within a single fluid transmission line, comprising the steps of:

(A) providing said combined laminar flow to a fluid mixer through a mixer input port;

(B) passing said combined laminar flow through a mesh material positioned inside said fluid mixer and thereby forming a mixture of said first and second fluids; and

(C) outputting said mixture of said first and second fluids from a mixer output port.

37. The method of claim 36, wherein said first fluid is whole-blood and said second fluid is a medicinal solution.

38. The method of claim 37, wherein said mesh has a hole size between 100 and 600 microns.