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(54) Title: RECIPROCATING TANGENTIAL FLOW FILTRATION METHOD AND APPARATUS CASSETTE

(57) Abstract: Reciprocating tangential filtration device for micro and ultrafiltration of volumes, from milliliters to liters utilizing positive displacement pumps. Internal mixing features disrupt the laminar flow patterns enhancing the filtration process. Direct connection of the pumps to the cassette provides a closed sterile system design providing complete control of the pressure and flow parameters. This control allows the process parameters to be adjusted during the filtration process optimizing the process. This scalable method of tangential flow filtration, utilizing low pressures, minimizes physical stress, shear or mechanical damage to the specimen. The applications for biochemistry into life sciences; sample preparation, cell culturing, fermentation, custom biological therapeutics and chronic wound care utilizing the filtration for the harvesting and concentration of platelet growth factors for autologous applications in the laboratory or bedside applications of the process. The method is gentle, precise, rapid, low cost and disposable.



Description:

RECIPROCATING TANGENTIAL FLOW FILTRATION METHOD AND APPARATUS CASSETTE

- 001 The invention relates to processing bioactive, biological or other materials of a fragile nature. Specifically separating these materials during processing of blood plasmas, to harvest cellular materials, proteins, antibodies, cytokines or molecules, the liquid or broths produced in fermentation and cell culturing by the cells. It may be applicable to any fragile long chain organic or inorganic molecule preparation process where separation is required
- 002 Tangential flow filtration is widely used for processing biologics. These systems are designed to process large volumes at high pressures and flow rates. Few address the small volume applications. These applications require different methods to protect the specimens from damage which will alter the final product.
- 003 Reciprocating tangential filtration is a method of micro and ultra-filtration for small specimen volumes, from fractions of a milliliter to a few liters. The advantage of this invention is it is a quick, gentle method of separating liquid and solids. Where the specimen pumps connect directly to the filter cassette minimizing the system dead space.
- 004 The internal flow channel mixing/turbulence reduces or eliminates the laminar flow patterns and increases the flow against the membrane surface improving the self-cleaning actions and the filtration rates. The filtration process is continuous as the filtration is performed in both directions. The turbulence patterns change as the direction of the flow changes.
- 005 Sequential or selective filtrations to isolate a cell or particle of a given size can be performed by utilizing two or more membrane sizes. This procedure is performed by filtering a specimen then re-filtering either the remaining specimen or the filtrate. Wash or rinse solutions may be injected into the system to keep the specimen fluidic and filterable.
- 006 It minimizes the physical damage to the specimen because it is performed without mechanical pumps or high pressures. It is a low cost simple method of filtration. It eliminates exposure to the materials being processed, as it is a closed system. It allows the variation of both the flow rate and pressure during the filtration cycle to optimize the parameters to the materials being filtered. This makes tangential filtration available to laboratories that requires quick, gentle, precise and cost efficient sample preparation of bioactive or fragile materials.
- 007 The system comprises of two main components these are: filter

cassette, filtration module. The cassette is the actual filter device and the module is the mechanism which operates the filtration process. The system may be devised to function in several levels from manual to fully automated.

- 008 The filter cassettes design is a top piece, a bottom piece and filter membrane. The top piece has two ports that extend outwardly on one side. These ports are the inlet and outlet passages for the specimen to flow through. The opposite side of the top piece contains a flow channel recess, which connects the two ports. The flow channel recess becomes a chamber when the filter material is assembled between the two molded pieces. Located in the flow channel are multiple ribs positioned crosswise to the flow directions. As the specimen flows through the flow channel and across the ribs a turbulence is created in the specimen flow pattern that disrupts the laminar flow patterns that normally occur in linear flowing systems. The second molded piece the bottom piece contains a collection grid, which is of similar size and shape of the flow channel of the first piece that contains membrane support ribs and filtrate outlet port extends outwardly on the opposite side. The area surrounding the flow channel and collection grid is the sealing surface. The third piece is the filter material. The filter is hermetically sealed to the top and bottom pieces. The filter material preferred embodiment is the track-etched membrane, because of the smooth surface and the precise pore sizes, other filter materials may be used.
- 009 The filtration cassette may be operated manually utilizing one or more positive displacement pumps or be devised as semi-automated or automated devices. The simplest embodiment is a single pump cassette that utilizes a collection chamber positioned on the opposite port which collects the specimen as it exits the flow channel. As the specimen fills the chamber the chamber becomes pressurized. This pressure is used to return the specimen back through the flow channel and into the pump for the return cycle of the filtration process. In two pump operations the second port is connected to a second pump which collects the specimen after it is pumped through the flow channel. The positive displacement pumps may be embodied in several designs. These are syringes, bellows or diaphragm pumps. Any method that will not cause physical stress shear mechanical damage to the liquid/solid mixture as is the case with impeller pumps and peristaltic pump rollers.
- 0010 The use of two pumps provides several features: The system is completely closed; No exposure to biohazardous materials. Filtration pressure and flow control of the specimen; Coordination of the movements of the two pumps with load sensors or by sensing the motor drive currents. The first pump or bellows is moved, pushing the specimen into the first port and into the cassette flow channel, the amount that the plunger is moved before the second pump begins to move in the opposite direction to receive the specimen

creates a predetermined pressure. In some cases (i.e. biological materials) a low pressure may be required to minimize damage to cellular or protein components and in other cases (i.e. inorganic chemistries) a higher pressure would be used to reduce the filtration cycle time. This cannot be done in the prior art as taught in 4,695,430, 4,818,493, 5,000,923, 6,398,956, 6,740,240, 6,926,834, 7,288,195 which pressure is applied to the specimen and the flow is only minimally restricted by the flow channel. These devices are limited to a narrow pressure range to avoid massive failures.

- 0011 The semi-automated or automated filter module is comprised of one or more drive motors that apply force to the pumps to move the specimen into and through the flow channel to the opposite pump or chamber. These may be lead screw, ball screw, or magnetic rail type linear drives. The pumps are microprocessor controlled through operator inputs and system sensor data. The operator inputs will include the pump type/size, optimum pressure, maximum pressure, the flow rate, maximum filtration cycles and or the liquid mixture to be filtered. From some of these inputs the filtration cycle parameters will be calculated. Other inputs shall be used to modulate the pumping speed and pressure to maintain the optimum process conditions throughout the filtration cycle. The flow rate is controlled by the drive speed, the pump size and the flow channel dimensions. The pressure is the result of the flow channel size and pressure applied to the pump.
- 0012 The system will contain sensors to monitor the force applied to the bellows or pumps the rate of flow and the size of the flow channel in combination with the sensor input will be used to control the force on the specimen being filtered. Disposable pressure sensors are available that can directly monitor the system pressure. Constant feedback from the plunger pressure transducers monitors the system performance and adjusts operating parameters to optimize the filtration cycle to maintain consistent output that will not cause physical stress, shear or mechanical damage to the liquid/solid mixture. The data of the filtration cycle may be recorded and provided as documentation of the process for cGMP or ISO regulatory requirements.
- 0013 There will be several filter cassettes for the range of volumes from fractions of a milliliter to several liters. Each filter cassette will fitted with a number of filter membranes for various filter requirements. Each filtration module can accommodate several cassette sizes.

What is claimed is:

1. A filter cassette capable of receiving a fluid specimen, , with internal mixing in the flow channel, powered by one or more positive displacement pumps comprising of three pieces a top piece, a bottom piece and a filter;
 - a top piece according to claim 1 comprising of one inlet port and a closed chamber or more than one inlet ports connected by a flow channel;
 - a flow channel according to claim 1 shall have a height of .001 to .025 inches or greater, preferably .004 to .010 inches;
 - a flow channel according to claim 1 contains ribs positioned across the direction of flow which are 2 to 50 percent the height of the flow channel, preferably 5 to 25 percent;
 - a bottom piece according to claim 1 comprising of a collection area for receiving the filtrate;
 - a collection area according to claim 1, comprised of one or more outlet ports which the filtrate is discharged through to a collection container;
 - a collection area according to claim 1 contains ribs that support the membrane to create an irregular non-flat surface when pressure is applied, the ribs are positioned in a radiating array directed away from the outlet port;
 - three components according to claim 1 that comprise the filter cassette are hermetically sealed to each other;
 - a flow chamber according to claim 1 may be a single channel, parallel channels, serpentine or spiral to increase the filter area while retaining the width – length aspect ratios and controlling the specimen flow across the filter;
2. a module consisting of positive displacement pump or pumps according to claim 1 may be manually driven or powered by linear motors with force sensors;
 - A cassette is directly connected to one or more positive displacement pumps which move the specimen into the filter cassette, through the flow channel and into a chamber or second positive displacement pump, additional ports may be used for the addition fluids required by the process;
 - The filter action is a reciprocation tangential flow where the flow occurs between the two ports of the top piece or a single port and a closed chamber, across the membrane surface with gentle turbulence induced by the flow channel ribs;
 - the flow according to claim 1 the ribs located in the top piece flow channel and in the bottom piece membrane support create an irregular flow channel of varying heights, the irregular heights along the flow path disrupt the laminar flow pattern;
 - the filtration process is continuous as the filtration is performed in both directions. The turbulence patterns change as the direction of the flow changes;
 - the ribs according to claim 1 provide gentle turbulence to the specimen flow and movements of the solids in the sample increasing the cleaning

action and increasing the filter function, functional life and utility of the cassette;

the membrane support ribs according to claim 1 allow micro flexing of the membrane to dislodge particles lodged in the filter pores;

the cassette according to claim 1 with the positive displacement pumps, according to claim 2, provides for full control of filtration pressure and flow rates for optimum control of the filtration process;

The filter module automates the filtration method to maintain the filtration parameters for optimum performance comprised of one or more positive displacement pumps and pressure transducers, and microprocessor controller with operator interface;

3. A system controller, microprocessor based unit that monitors the sensor inputs to optimize the filtration cycle, and provide full automation to the system operation;

the positive displacement pump drive according to claim 2 will be a motor driven linear drive preferably a stepper motor and each will include a force transducer to monitor the drive force, the filtration pressure is calculated from the drive force and pump size and cassette size;

module controller performs the filtration process according to claim 3 monitors the system performance and adjusts operating parameters to optimize the filtration cycle to reduce physical stress, shear or mechanical damage to the specimen while operating within the predetermined ranges;

a module according to claim 2 that comprises one or more linear drive devices which move the positive displacement pumps that pump the specimen through the filter cassette in two directions with process controls;

the controller according to claim 3 receives operator inputs of cassette type pump type and size and operating parameters such as pressure ranges and flow rate ranges are used determine the filtration procedure;

the controller according to claim 3, utilizes feedback from the plunger pressure transducers, operator inputs of cassette type pump type and size and operating parameters are used to modulate the pressure and flow for optimum filtration conditions;

the controller according to claim 3 can store filtration procedures, specimen and cassette parameters for recall and record the actual filtration process data for permanent record to meet regulatory requirements;