Application Note

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Leading Process Analytics

Efficient Normal Flow Filtration

Through Controlled Pressure Solutions

Normal flow filtration (NFF) plays a crucial role in eliminating bacteria, viruses, and colloidal material from biopharmaceutical operations. NFF is used extensively, up to 40-50 times, during seed culture propagation to final vial filling. Given its prevalent use, it is crucial to have effective regulation and supervision of the process. METTLER TOLEDO Pendotech provides innovative solutions to enhance biopharmaceutical operations. Our Peristaltic and Diaphragm Pump Modules, and Single-Use Pressure Sensors allow precise monitoring and control of NFF processes for optimal filtration performance and maximum yield. METTLER TOLEDO Pendotech's Filter Screening System enables up to four simultaneous experiments, ensuring efficient and comprehensive results.

Background

Normal flow filtration is a widely used conventional filtration method that has applications in various industries, including pharmaceuticals, biotechnology, and food and beverage. It is employed for sterile filtration of fermentation media, buffers, and product proteins and is effective in separating and purifying biomolecules such as proteins, viruses, and antibodies. NFF plays an essential role in primary and secondary clarification during the manufacturing of microbial and mammalian cell-based biotherapeutics. As a unit operation, NFF is a valuable tool utilized for numerous applications, making it a critical process in many industries [1].

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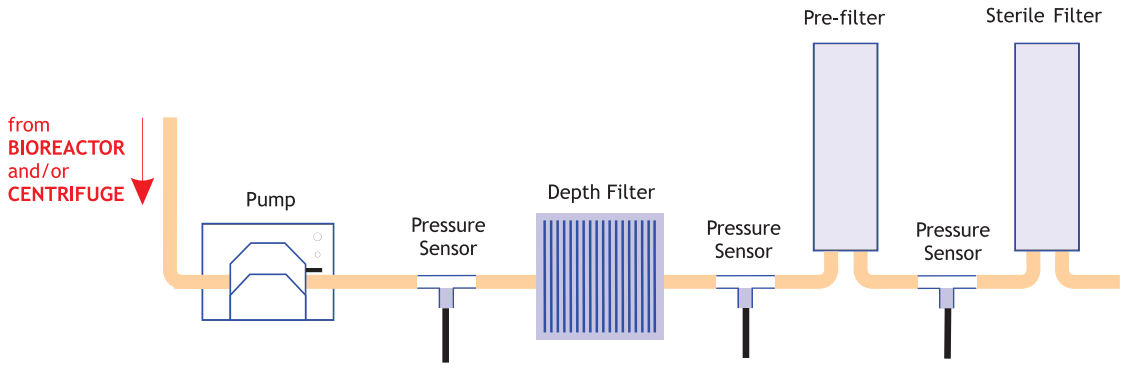


Fig. 1 Single Normal Flow Filtration Train

Process

NFF is a batch process in which the complete feed flow passes through a semipermeable membrane, allowing smaller molecules to pass through while retaining larger molecules at the membrane surface [2]. This method is commonly used in the biopharmaceutical industry for polishing final products or protecting downstream operations. It offers several advantages that make it a suitable method for various applications. Firstly, NFF operates at low shear rates, making it a gentle process that minimizes the risk of damaging sensitive molecules or cells during filtration. Additionally, NFF allows efficient recovery of target molecules as the entire feed volume passes through the membrane [3]. The system is simple to set up and operate, making it suitable for both research and large-scale processes.

Challenges

Despite its advantages, NFF also has some limitations that should be taken into consideration. The membrane can become clogged with retained particles, which reduces filtration efficiency and may require regular cleaning or replacement to maintain optimal performance. Additionally, the membrane's pore size limits the retention of larger molecules, making it more suitable for retaining small to medium-sized particles. It is a pressure-driven process, where a positive pressure gradient is applied to the feed solution to drive it through the membrane. This applied pressure is necessary to overcome the hydraulic resistance of the membrane and to maintain the flow rate. However, variations in the applied pressure can significantly impact filtration performance. If the applied pressure is too low, the flow rate will be reduced, and filtration will take longer.

Conversely, if the applied pressure is too high, the membrane can become damaged, which can lead to a loss of filtration efficiency and reduced product yield. Therefore, maintaining a consistent and appropriate pressure is critical to ensuring optimal filtration performance and yield. Regular monitoring of pressure during the NFF process can help to identify and address any pressure-related issues promptly, ensuring that the process runs smoothly and efficiently.

Solution

METTLER TOLEDO Pendotech's Filter Screening System is a valuable tool for optimizing normal flow filtration processes. The system is designed to conduct volume throughput studies with constant flow or constant pressure. It allows for the operation of up to four trains in parallel with up to three pressure measurements per train. A graphical user interface (GUI) streamlines user interaction with the process. The system interfaces with up to four pumps for independent control of each pump, and automation allows for unattended operation - individual pumps will shut off when a volume target is reached, or an alarm occurs. Total flow can be measured either by scales with the ability to enter density to convert weight to volume or by pump accumulation. Alarms for high pressure for each train and high delta pressures for each filter will shut the pump off for that train. The system also allows for real-time calculation of flux and permeability based on the entered filter area within the GUI, as well as the ability to view a wide variety of trends real time with an instant export feature of the current trend view. Process data acquisition, including filter and train names, key experiment information, and notes, is saved in a .csv data file that can be opened with Excel. The system also can run four parallel constant pressure experiments by use of scale input functionality. Pendotech Pressure Sensors with luer fittings connecting directly to filter test devices or larger sensors with sanitary flange or barb can be used.

The system logs individual pump run times for management of pump maintenance and/or tubing changeouts. The FLOW-ADJUST feature allows the GUI to automatically control a filter DeltaP setpoint, and the option to serve data to OPC clients such as PI from OSIsoft® is also available. The Filter Screening System enables efficient parallel experiments, real-time data collection and analysis, and optimized filtration processes. This system greatly enhances the accuracy, efficiency, and reliability of filtration studies.

Core NFFSS consists of:

Pumps	Pumps play a crucial role in integrated systems used for constant flow experiments, such as those involving Pmax. Pendotech offers two pump modules - the Peristaltic Pump Module and the Diaphragm Pump Module, each with unique characteristics and packaged in a compact form factor to minimize the bench space required for a full-featured setup. Apart from these, third-party pumps like those offered by Masterflex and Watson-Marlow can also be used. This option provides a more flexible setup since the pumps can be used for other purposes when not in use with the system.
Scales	The measurement of the filtered material amount is done through the scales integrated into the system. In constant flow applications, the scale function can be disabled, and the filtered volume is automatically measured by pump totalization based on the flow rate setting. However, for constant pressure applications such as Vmax, scales are needed to measure the cumulative volume versus time. In addition, a pressure vessel is also required for constant pressure experiments. Pendotech provides an option for constant pressure experiments that features a low hold-up volume, precise pressure regulation, and pressure recording capability.
Pressure sensor	Pendotech Pressure Sensors come in different sizes, but the ones with luer fittings are typically the preferred choice. These luer sensors offer low hold-up volume and are available in polycarbonate, which can also be obtained as a sterile option. Alternatively, the polysulfone version provides superior chemical resistance and is compatible with NaOH. Sanitary flange sensors are also available for direct connection to filters with flanged connections. Additionally, Pendotech offers hose barb sensors in sizes ranging from 1/8″ to 1″, which can be integrated with flexible tubing.

Control box	The Control Box serves as the "brains" of the system. It reads the pressure sensors and scales to control the pumps and all settings are stored in its memory. The Control Box also monitors endpoints and alarms while the system is running.
PC with software	Users interact with the system through a PC running custom Filter Screening System GUI software. The software communicates with the control system by receiving all data for viewing and storage, updating parameters in the control system via user interaction, and optionally serving data to OPC clients such as a data historian and PI from OSIsoft®.

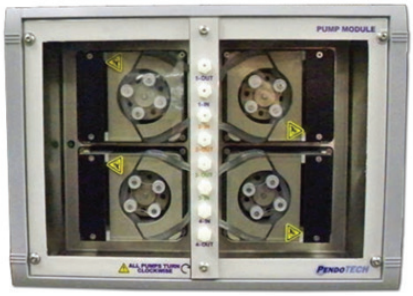
Pressure is a critical parameter to measure for indicating filter performance and capacity. Excessive pressure, caused by high protein concentration or flow rate, can result in particulate accumulation on the membrane surface, forming a thick filter cake that obstructs the membrane and impedes the filtration process. However, this issue can be minimized by utilizing in-line sensors along with the appropriate control strategies to control and optimize the filtration parameters, allowing for increased efficiency and higher yield. As pressure is a key variable in filtration processes, measuring pressure data is an essential aspect of any experimental design. Integrating a pre-calibrated pressure sensor in the feed line of a filter is an added feature that can further improve the accuracy and reliability of pressure measurements [4]. METTLER TOLEDO Pendotech's Single Use Pressure Sensors™ are available in various options for fittings, including luer fittings for direct connection to filter test devices and larger sensors with sanitary flange or barb fitting.

METTLER TOLEDO Pendotech offers a diverse product portfolio that includes Diaphragm and Peristaltic pump modules, both of which are suitable for use with the Normal Flow Filtration Screening System depending on the specific requirements of the bioprocess application.

Diaphragm Pump Module

- Low shear, long life diaphragm pump technology
- Minimal drop in flow while pumping against back pressure
- Stepper motor control "Rapid Intake" stroke technology that minimizes pulsation
- Space-saving design with quiet operation
- Precise pumping from 2.0 mL/min to 100 mL/min
- Low internal hold-up volume
- Broad range of chemical compatibility (product contacting internal pump components are all fluoropolymer-based)
- May be run dry

Peristaltic Pump Module



- Peristaltic design with easily changeable fluid path that uses commonly available tubing
- Minimal drop in flow while pumping against back pressure
- Stepper motor control technology that pumps precisely
- Space-saving design with quiet operation
- Precise pumping from 1 mL/min to 120 mL/min
- May be run dry

In addition, our system provides an expansion option for inputting up to two additional analytical measurements per train, such as temperature, turbidity, UV absorbance and pH. This is made possible through the Analog Inputs Connector located on the back panel, further enhancing the versatility and functionality of our NFF system.

At METTLER TOLEDO Pendotech, we have developed an innovative solution to address the issue of membrane fouling, which can reduce filtration efficiency and lifespan. Our NFF system includes peristaltic or diaphragm pumps integrated with the filtration system, ensuring maximum efficiency and extended membrane life. This advanced system is designed for producing high-quality biopharmaceuticals efficiently and effectively. It features Pump Modules and a PC-based GUI that provides precise control over liquid flow into the filtration column for continuous and seamless filtration. The system is expandable through additional analog inputs, allowing for external measurements alongside other process data. This provides an integrated solution for streamlined normal flow filtration. Our system offers the added advantage of conducting four independent experiments, making process optimization easier than traditional NFF methods. With its specifications, our system is highly effective in delivering reliable and consistent outcomes, making it an excellent choice for biopharmaceutical filtration needs.

References:

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