Application Note

PENDOTECH
Leading Process Analytics

Improve Perfusion Cell Culture
With Controlled Pressure and Flow Rate

Perfusion bioreactors are adaptable systems in biopharmaceutical production and regenerative medicine, facilitating continuous generation of biologics and simulating physiological environments for improved tissue development. These bioreactors enhance cell growth by regularly providing fresh media and removing depleted media, improving viability and productivity. Monitoring and controlling pressure and flow within these setups is vital for maintaining stable conditions, as variations can negatively influence yields.

Background

Perfusion bioreactors are highly adaptable systems with wide-ranging applications in various sectors [1]. They play a crucial role in biopharmaceutical manufacturing by enabling the continuous production of biologics, such as monoclonal antibodies, leading to enhanced yields and helping to ensure consistent product quality. In regenerative medicine, perfusion bioreactors mimic physiological conditions, fostering improved tissue development and integration.

METTLER TOLEDO

Process

Perfusion cell culture is a continuous bioprocessing technique primarily utilized in biopharmaceutical manufacturing. The process starts with cell seeding, where cells are introduced into a bioreactor filled with growth medium. Unlike conventional batch processes, perfusion allows for the ongoing exchange of medium: fresh medium is added while spent medium and cellular waste are removed. A filtration system keeps the cells contained within the bioreactor. This constant supply of fresh medium ensures an uninterrupted flow of nutrients and carbon sources, which is crucial for sustaining high cell densities and viability. Furthermore, the removal of spent medium helps maintain a stable environment, reducing the likelihood of nutrient depletion and toxic by-product accumulation.

Throughout the perfusion process, the biopharmaceutical product is collected continuously, enabling efficient downstream processing. These systems can operate for extended durations, from weeks to months, resulting in enhanced volumetric productivity. The process can be scaled up for clinical and commercial production while ensuring the quality of the product is upheld. Overall, perfusion cell culture presents significant benefits over traditional batch methods, such as increased cell densities, longer culture durations, and improved product quality, making it an essential technique for the production of therapeutic proteins and other biopharmaceuticals.

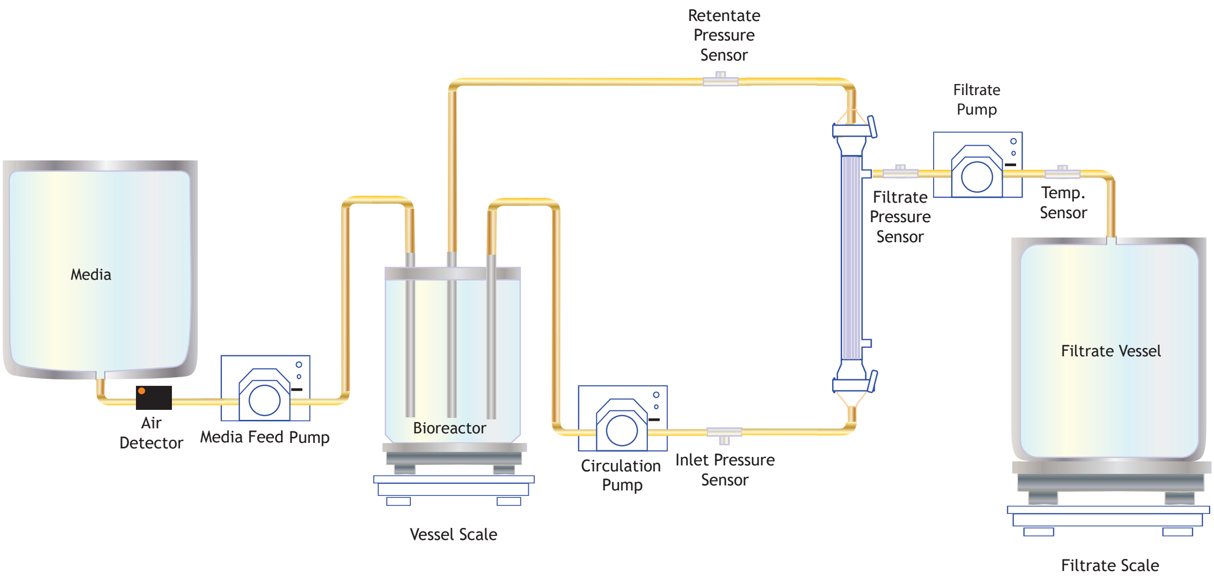

Fig. 1 Schematic diagram of in-line perfusion products and sensors

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Challenges

Controlling pressure within perfusion bioreactors is essential for maintaining optimal cell growth conditions and ensuring a stable physical and chemical environment. Continuous monitoring of pressure can help identify issues such as blockages or leaks, preventing potential system failures and ensuring uninterrupted operations. Consistent pressure is crucial for producing uniform products, as fluctuations can negatively affect both cell growth and overall yields.

In the perfusion process, maintaining ideal pressure and flow rates before the hollow-fiber cartridge is necessary for ensuring effective nutrient delivery and waste removal for the cells. Correct pressure control prevents damage to the delicate fibers in the cartridge, as excessive pressure can cause ruptures, leading to contamination and reduced filtration efficiency. Additionally, fluctuations in pressure can create turbulent flow, stressing the cells and compromising their viability. Maintaining appropriate flow rates ensures even distribution across the filter's surface, which is essential for preventing channeling and ensuring effective filtration.

Throughout operation, biological systems are inherently dynamic, influenced by factors such as cell proliferation and metabolic changes that can affect pressure and flow conditions. Continuous monitoring is vital for preserving performance and maximizing the efficiency of the bioprocessing environment. Real-time data on pressure and flow is essential for adapting to changes in the biological system, allowing operators to adjust parameters promptly to maintain optimal conditions.

Pressure sensors are fundamental for the effective functioning of these systems. An inlet pressure sensor will track the pressure of incoming fluids. Appropriate adjustments ensure pressure remains at appropriate levels to maintain flow rates and protect the bioreactor. In contrast, a retentate pressure sensor measures the pressure of fluids after filtration, providing insights into filtration performance and preventing clogging. Transmembrane pressure, calculated from both inlet and retentate pressures, is an important measure of the pressure differential across the filter membrane, influencing filtration efficiency and cell retention. In-line pressure sensors therefore provide real-time data that enables necessary adjustments, optimizing performance and consistency throughout perfusion.

Solution

Pressure Sensors

METTLER TOLEDO Pendotech's Single-Use Pressure Sensors deliver precise measurements of static and dynamic pressure for gases and liquids in biopharmaceutical processes. These sensors are ideal for disposable applications and are a reliable alternative to stainless steel pressure transducers.

The pressure sensors, equipped with High Accuracy Pressure (MEMS-HAP™) chips, are ideal for monitoring filtration, chromatography, and bioreactors. They come with hose-barb connections that range from 1/8 to 1 inch (3.175 mm - 25.4 mm), as well as sanitary flange and luer connections. Designed for repeated cleaning and re-use, these sensors operate within a pressure range of -11.5 to 75 psi (-0.79 to 5.2 bar). Their clear flow path and absence of dead legs result in reduced hold-up volume compared to traditional stainless-steel transducers or gauges. The sensors have varying accuracy levels based on the pressure being measured: ±2% for readings from 0 to 6 psi, ±3% for 6 to 30 psi, and ±5% for 30 to 60 psi.

Made from either polycarbonate or caustic-resistant polysulfone, all materials in the fluid path comply with USP Class VI requirements both before and after irradiation. Each lot includes a Certificate of Quality, and individual NIST Certificates can be requested. The sensors are manufactured in an ISO 9001 certified facility with an ISO Class 7 clean room and are compatible with gamma and X-ray irradiation. Additionally, they feature a test port for non-invasive testing in place.

Flow Meters

METTLER TOLEDO Pendotech specializes in precise flow measurement solutions for bioprocessing applications and offers a variety of flow meters and monitors. Our high-accuracy Coriolis Flow Meter is unaffected by changes in viscosity and conductivity, and its compact design makes it versatile for different applications. These flow meters are crucial in purification processes, providing 1% precision.

The Single-Use Rotary Flow Meters provide an accurate way to measure flow in processes. When used with tubing, they serve as a low-cost alternative to reusable rotary flow meters. Equipped with advanced DSP technology, these meters ensure reliable performance even in challenging conditions and integrate seamlessly into OEM equipment. Our single-use flow meters are made from biocompatible, gamma-sterilizable polypropylene and comply with FDA and other regulations. Suitable for long-term applications, the Single Use Rotary Flow Meters connect to monitors via a 3-foot cable, making them a practical choice for various processes.

Conclusion

Improving perfusion cell culture through monitoring and controlling pressure and flow rate is essential for maximizing cell viability and productivity in biopharmaceutical production and regenerative medicine. Researchers and manufacturers can maintain stable operating conditions by utilizing advanced pressure sensors and flow meters from METTLER TOLEDO Pendotech, ensuring efficient filtration and optimal media exchange. Real-time data capture, documentation, and tracking improve operational reliability and safeguard the consistent quality of biologics and tissues produced in perfusion bioreactors.

References

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