Application Note

PENDOTECH
Leading Process Analytics

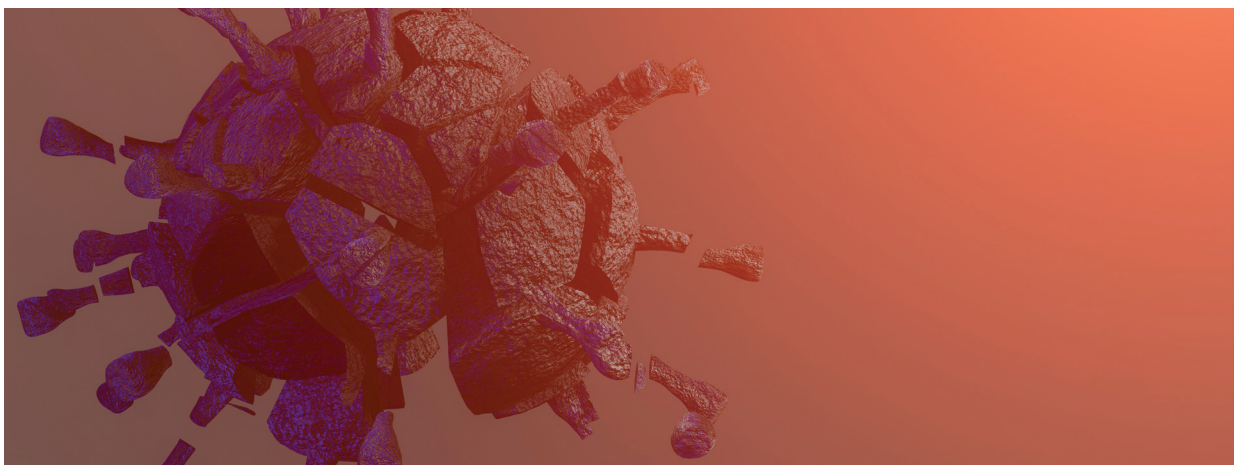
Enhancing Biotherapeutics Safety

With Advanced pH and Pressure Sensors

Low pH viral inactivation is essential for neutralizing enveloped viruses in biopharmaceuticals but poses challenges related to protein stability and accurate pH maintenance. Even minor pH deviations can affect either viral inactivation, product efficacy, or both. Continuous pH monitoring allows for real-time adjustments, preserving protein integrity and ensuring high product quality. Additionally, monitoring pressure in the viral inactivation chamber is critical for maintaining flow consistency and enhancing safety. Consistent pressure promotes adequate exposure to low pH, reducing variability and preventing inadequate mixing.

Background

Viral inactivation is a crucial step in bioprocessing that significantly enhances the safety of biotherapeutic products, such as vaccines and monoclonal antibodies, by rendering any viruses inactive and thereby protecting patients from potential disease. This process complements virus removal methods, such as filtration and chromatography, to provide comprehensive viral safety for the overall quality and efficacy of these therapeutic products.



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Process

Viral inactivation and removal are critical steps in the development of biotherapeutic products, such as monoclonal antibodies (mAbs) and polysaccharides. Common inactivation methods include low pH approaches and solvent or surfactant-based techniques. The choice of methods depends on factors like the product's size, type, purification processes, and the nature of the target viruses. To effectively implement these inactivation methods, the viral inactivation process in bioprocessing consists of several essential steps designed to ensure the safety and efficacy of biotherapeutic products [1].

Initially, the biotherapeutic product undergoes preparation, which may involve purification steps to eliminate impurities and concentrate the product. Next, the pH is adjusted, typically by adding an acid, to create an environment that disrupts viral particles. The product is then maintained at this adjusted pH for a specified duration for effective viral inactivation, as it varies depending on the type of virus and the product [2]. Following holding, the pH is neutralized to stabilize the product and prevent degradation. Additional purification steps, such as filtration or chromatography, may then be employed to remove any remaining viral particles and impurities. Finally, the product undergoes quality control testing to confirm that viral inactivation has been successful and that it meets all safety and quality standards. Once verified, the inactivated and purified product is transferred to the next stage of the bioprocessing workflow, such as formulation or final fill and finish. Each of these steps is meticulously controlled and monitored to ensure the overall safety and efficacy of the final product.

Maintaining pH during viral inactivation is crucial for ensuring the effectiveness and safety of the process, but it presents several key challenges. First, many biomolecules are sensitive to pH changes, and maintaining the correct pH is vital to prevent denaturation or degradation. Additionally, the choice of buffer system can significantly impact pH stability, necessitating the selection of a buffer that maintains the desired pH range throughout the process. [3] Various process parameters, including temperature, ionic strength, and protein concentration, can also influence pH stability, requiring careful control to achieve the desired conditions. Impurities and aggregates present in the process stream can further complicate the stability of pH and reduce the effectiveness of viral inactivation. Addressing these challenges necessitates diligent monitoring and control of process parameters to ensure successful viral inactivation while preserving product quality and safety.

Challenges

Low pH viral inactivation is vital for effectively neutralizing enveloped viruses in biopharmaceuticals, but it comes with several challenges that highlight the need for precise pH monitoring. These challenges include protein stability issues, where low pH can lead to aggregation and denaturation, negatively impacting product efficacy. Accurate pH levels at low pH must be maintained, as even slight deviations can compromise viral inactivation. Continuous pH monitoring allows for real-time adjustments, preserving protein integrity and maintaining high product quality. Advanced tools, such as high-precision pH sensors and automated control systems, are essential for achieving the required pH control.

In parallel to pH control, monitoring and controlling pressure at the inlet and outlet of the viral inactivation chamber is essential for the efficiency and consistency of the inactivation process. Consistent pressure ensures uniform flow, allowing for adequate exposure to the low pH environment, optimizing flow rates, minimizing process variability, and enhancing overall safety and product quality by preventing foam formation and maintaining product integrity. Real-time monitoring with pressure sensors is vital for maintaining the desired pressure range, as these sensors provide continuous feedback and enable immediate adjustments when pressure deviates from set parameters. The interplay between pressure and mixing is critical for achieving uniform viral inactivation; low process pressures can lead to inadequate mixing, preventing some viruses from being sufficiently exposed to the low pH, thereby reducing inactivation efficiency. Additionally, large pressure fluctuations can disrupt flow dynamics, resulting in uneven mixing and varying pH levels within the vessel, which may allow some viruses to survive. To maximize the effectiveness of viral inactivation, careful process design is crucial to ensure that the entire solution consistently maintains exposure to the low pH, thereby enhancing overall inactivation rates and product safety.

METTLER TOLEDO Pendotech's Solution

pH Sensor

METTLER TOLEDO Pendotech Single-Use In-line pH Sensors feature cutting-edge InSUS 307 pH probe technology, delivering accurate and dependable pH measurements for downstream bioprocessing applications. These sensors perform well in a pH range of 3 to 10, achieving an accuracy of ± 0.10 pH when operating within ± 1.50 pH units of a single-point process calibration. With a rapid response time of less than 20 seconds between pH 4 and 7, they can effectively monitor quick pH fluctuations caused by process variations. The InSUS 307 pH sensors are rated for temperatures ranging from 5 to 60°C and can withstand pressures of 4 bar at 25°C, 2 bar at 40°C, and 1 bar at 60°C, making them a versatile and efficient option for bioprocessing operations.

Pressure Sensor

METTLER TOLEDO Pendotech specializes in providing precise flow measurement solutions tailored for bioprocessing applications, featuring a range of flow meters and monitors. Our Coriolis Flow Meter offers high accuracy, remaining unaffected by variations in viscosity and conductivity, while its compact design enhances versatility across different applications. These flow meters play a critical role in purification processes, delivering 1% precision. Additionally, METTLER TOLEDO Pendotech's Single Use Rotary Flow Meters offer an accurate and economical solution for flow measurement in various processes. They present a low-cost alternative to traditional reusable rotary flow meters when used with tubing. Featuring advanced DSP technology, these meters ensure reliable performance even under demanding conditions and integrate easily with OEM equipment. Our single-use sensors are constructed from biocompatible, gamma-sterilizable polypropylene (PP) and adhere to FDA and other regulatory standards. Designed for high use, the Single Use Rotary Flow Meters connect to monitors via a 3-foot cable, making them a practical choice for a variety of processes.

Conclusion

In summary, viral inactivation is a critical component of bioprocessing that ensures the safety and efficacy of biotherapeutic products. By effectively disrupting viral structures through precise control of parameters like pH and pressure, the process not only protects patients but also enhances the overall integrity of the products. METTLER TOLEDO Pendotech's advanced pH and pressure sensors provide the reliability and accuracy needed to optimize this process, ensuring that biopharmaceuticals are produced safely and effectively. As the industry continues to prioritize viral safety, these innovative solutions will play an essential role in maintaining high standards of quality in bioprocessing.

References

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