Application Note

PENDOTECH
Leading Process Analytics

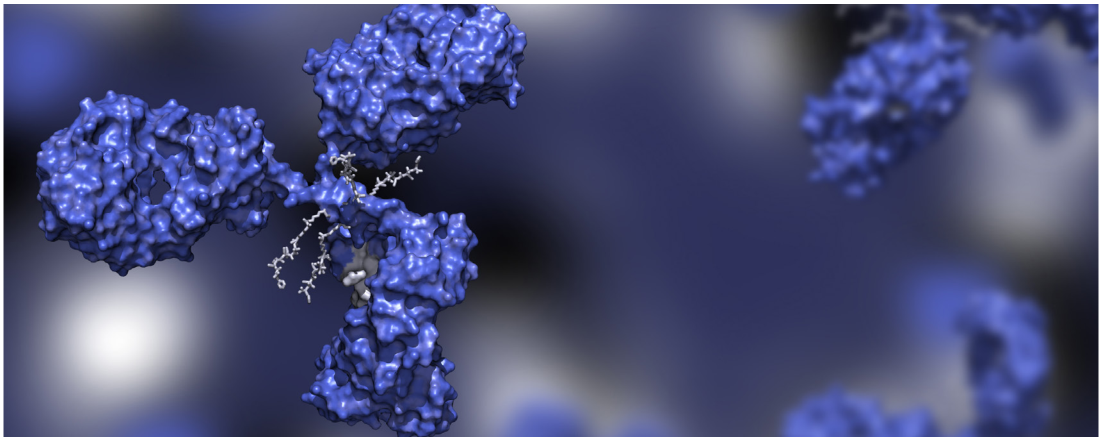
Enhance ADC Manufacturing
With Advanced Process Control

Antibody-Drug Conjugates (ADCs) are targeted cancer therapies combining monoclonal antibodies and potent drugs. Their production is challenging, especially purification, due to ADC heterogeneity and stability concerns. To ensure purity, stability, and regulatory compliance, advanced bioprocessing tools like high-precision flow meters, single-use in-line pH sensors, and highly accurate temperature sensors are essential for rigorous process monitoring and control.

Introduction

ADCs represent a sophisticated class of biopharmaceuticals, engineered for targeted cancer therapy. They consist of monoclonal antibodies conjugated to potent cytotoxic agents (payloads) via specialized linkers, designed to eliminate cancer cells while preserving healthy tissue. The attached payloads are directed to recognize specific antigens predominantly expressed on cancer cell surfaces. Upon binding to these antigens, ADCs are internalized by the cancer cell via receptor-mediated processes, allowing the intracellular release of the cytotoxic drug to precisely eliminate malignant cells with minimal systemic toxicity[1].

Compared to conventional chemotherapy, ADCs provide greater specificity, enhanced efficacy, and improved safety profiles. Over the past three decades, clinical studies have continually underscored the promising role of ADCs in treating both hematologic malignancies and solid tumors. Striking the right balance among innovations in linkers, payloads, and targeting mechanisms is critical in ADC design to optimize therapeutic outcomes, minimize side effects, and broaden their clinical applications.



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Process

The manufacturing process of ADCs is typically segmented into four key stages:
Antibody (Ab) functionalization, Conjugation, Purification, and Formulation. The initial two stages, Ab functionalization and conjugation, constitute the upstream phase, where the antibody is modified and linked to the cytotoxic payload. Following this, the downstream phase encompasses purification and formulation, ensuring the removal of impurities and preparing the final product for therapeutic use.

The purification process for ADC drugs begins with tangential flow filtration (TFF), specifically ultrafiltration diafiltration (UF/DF), which removes organic and conjugation-related impurities and facilitates buffer exchange. The UF/DF process effectively separates small molecular impurities due to their size being less than the membrane pore size, maintaining a process yield above 90%. This is followed by chromatography methods that exploit ADCs' unique physicochemical properties. Together, these purification steps ensure high-purity ADC products ready for formulation[2].

Challenges

ADC purification is challenged by the molecular complexity and heterogeneity of the product. Maintaining the stability of both antibody and cytotoxic payload throughout manufacturing is paramount. The conjugation introduces variability that requires sensitive and precise analytical sensors to monitor process parameters in real time. Key parameters influencing ADC purification include flow rate, pH, temperature, and buffer composition. Flow rate during TFF is crucial in ADC downstream processing, as it regulates shear forces and filtration efficiency. Optimal flow rates maintain membrane performance, reduce fouling, and prevent shear damage to ADC molecules. Too high flow rates risk aggregation and degradation, while too low rates decrease filtration flux and prolong processing time.

Temperature control is vital for maintaining ADC stability during chromatography. Elevated temperatures can cause degradation, linker cleavage, or aggregation, compromising safety and efficacy. Thus, chromatography is done at mild, controlled temperatures to preserve ADC integrity and activity.

The pH of chromatography buffers is key to controlling charge interactions between ADCs and resin. Maintaining optimal pH ensures effective binding and elution, reduces nonspecific interactions, and preserves ADC stability, preventing aggregation or linker hydrolysis that could affect product quality.

Overall, tight control and monitoring of flow rate during TFF, together with temperature and pH during ADC chromatography, are essential to achieve high-purity products with maintained stability, potency, and safety profiles. These measures help fulfill stringent regulatory requirements and ensure clinical success[2].

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Flow meter:

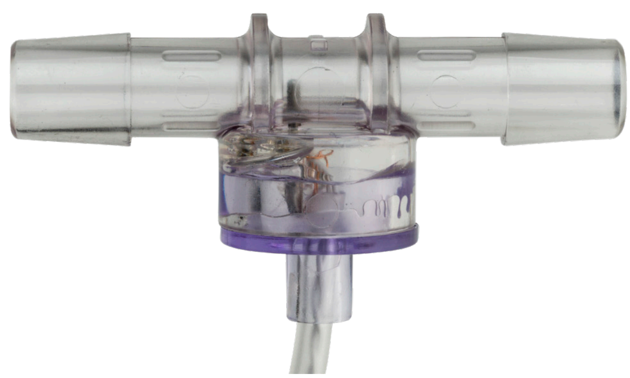
Flow meters are essential in many purification processes, offering high-precision flow measurement with 1% accuracy. These sensors can be either single-use to prevent cross-contamination or reusable. Their design without moving parts eliminates particle generation, making them ideal for applications requiring strict cleanliness. Equipped with DSP technology, these flow meters provide enhanced resistance to bubbles. They are easily integrated into OEM equipment, providing convenience for users. The single-use sensors are made from biocompatible, gamma-sterilizable polypropylene (PP), meeting FDA, USP-VI, BSE/TSE, and animal-free standards.

pH sensor:

Our Single-Use In-line pH Sensors feature advanced InSUS™ 307 pH probe technology, ensuring accurate and reliable pH measurements for downstream bioprocessing. They operate precisely within a pH range of 3 to 10, with an accuracy of ± 0.10 pH when operating within ± 1.50 pH units of the 1-point process calibration point. With a rapid response time of under 20 seconds between pH 4 and 7, these sensors effectively detect quick pH changes during processing. They are designed to function across a temperature range of 5-60°C and withstand pressures of 4 bar at 25°C, 2 bar at 40°C, and 1 bar at 60°C, making them a versatile and reliable solution for bioprocess applications.

Temperature sensor:

Single-Use Temperature Sensors deliver precise temperature readings specifically designed for single-use processes, minimizing contamination risks while maintaining durability for repeated cleanings. Perfect for in-line applications like filtration, chromatography, TFF, filling, and process monitoring, these sensors work seamlessly with devices such as the TEMP-340 handheld unit, PDKT-TT monitors, and other certified third-party equipment. Equipped with reusable cables and offered with hose-barb fittings, 1-inch sanitary flanges, or luer fittings, they ensure smooth fluid flow. Their thermistor elements provide a stable temperature-to-resistance profile, removing the need for calibration. With high sensitivity and accuracy—typically better than ±0.2°C (often ±0.1°C) over a 0-70°C range—these sensors are constructed from polysulfone (hose-barb and flange versions) or polycarbonate (luer fittings) and comply with USP Class VI standards. Manufactured in an FDA-registered, ISO 9001 certified facility, each sensor includes a quality certificate.



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Conclusion

The integration of advanced sensors and precise process control is essential for the scalable and reliable manufacturing of high-quality ADCs. By continuously monitoring critical parameters such as flow rate during TFF, and pH and temperature during chromatography, manufacturers can ensure ADC stability, purity, and therapeutic efficacy. METTLER TOLEDO's flow meters, single-use pH, and temperature sensors exemplify cutting-edge technologies that support these stringent requirements. Together, these solutions facilitate consistent, high-yield purification processes, enabling the production of potent and safe ADC therapies to meet the evolving needs of cancer treatment.

References

1. Antibody–Drug Conjugates (ADCs): current and future biopharmaceuticals
2. Review of Antibody Drug Conjugate (ADC) Purification - BOC Sciences

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