Disposable Bioreactor Sensors

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Abstract

Sensors that offer online information about the process state are necessary for modern bioprocess monitoring. Particularly, sensors for single-use bioreactor bioprocess monitoring are required due to the growing significance of disposable systems in biotechnological applications. These single-use bioreactors have different requirements for the sensors than traditional reusable bioreactors. For instance, a long lifespan or resistance to steam and cleaning methods are less important considerations, whereas the cost of sensors for disposable bioreactors is affordable on a per-use basis. Here, we give an overview of the most recent and cutting-edge sensors for single-use bioreactors, arranged according to how the sensor systems connect to the bioreactor. Non-invasive, in-situ sensors based on electromagnetic, semiconducting, optical, or ultrasonic measurements are the main area of focus. New technologies are also introduced, such as free-floating sensor spheres and radio-frequency identification sensors. Notably, the sensors presented here do not currently have a common interface for single-use bioreactors. Manufacturers should fix this flaw in the future to support single-use bioprocess monitoring and control.

Keywords: Bioprocess monitoring • Disposable bioreactors • Disposable sensors • Process analytical technology • Process control • Sensor systems • Single-use

Introduction

The biopharmaceutical sector now uses single-use bioreactors (SUBs) often. They have taken the role of conventional stainless steel reactor systems in many manufacturing facilities, particularly for the manufacture of high-value products in small volumes. When Good Manufacturing Practice (GMP) criteria are adhered to, disposable reactor technology offers enhanced facility flexibility with cheaper investment and energy costs, as well as a simpler manufacturing process because complex and labor-intensive cleaning procedures are rendered unnecessary. Today's market offers a variety of disposable bioreactor systems that can accommodate culture volumes ranging from a few mL (such as Micro-24, Pall Corporation, Port Washington, USA; ambr® systems, Sartorius Stadium Biotech, Göttingen, Germany) to 2000 L (such as Biostat® Cultibag STR, Sartorius Stedim Biotech, Göttingen, Germany). To ensure adequate mixing of all nutrients inside the reactor system and to supply an effective gas exchange into the medium, these systems are swirled, shaken, or pneumatically blended. Although mostly used for mammalian cell culture, it has been proven that yeast and other microbes can be grown in a disposable bag reactor. Lopez et al. and Eibl et al. review articles provide overviews of the available systems [1-5].

For better comprehension, control, and optimization, a thorough grasp of bioprocesses is required. Improved sensor concepts have been researched over the last 20 years based on the Process Analysis Technology (PAT) initiative of the US Food and Drug Administration (FDA) with the aim of monitoring the physical environment (e.g., temperature, shear stress), the chemical environment (e.g., substrate and product concentrations), and the biological system itself. Sensor designs for this kind of bioreactor are urgently required in order to further enhance the utilisation of disposable bioreactor technology.

In general, there are three different types of sensor applications: in-line, at-line, and off-line. In-line or in-situ sensors are in direct contact with the process media and are connected to the reactor. At-line systems rely on a sample that is taken out of the bioreactor and examined elsewhere. If data are continually captured and the sensor signal's response time is brief compared to the dynamics of the process, the measurement of in-line or at-line sensors can be regarded as being on-line. Off-line measurement is defined as any other measurement [6-10].

Discussion

Interface category

Sampling systems: Samples from disposable bioreactor processes can be analysed using ex situ sensor systems with probes for cell-free or cell-containing sampling. Additionally, by integrating a bioreactor bypass, these sampling probes can be used to link at-line analytical instruments to the bioreactor. Maintaining sterility while providing a representative sample stream for regular examination is sampling ports' biggest problem.

Through integrated sampling ports, cell-containing samples from disposable bioreactors are gathered. The majority of disposable bioreactor systems come with an aseptic connector or a thermoplastic welding tube sampling port. Sample containers that have already been pre-sterilized are joined together by welding and then sealed by heating. There are containers ranging in size from a few mL to 1 L. Aseptic connectors have the benefit of requiring no welding equipment, however the majority of manufacturers employ proprietary techniques that restrict flexibility.

In-Situ disposable sensors

The foundation of this interface is a single-use sensing component that is built into the reactor during production and sanitised with the SUB, typically using radiation. To connect the sensing element on the inside to the transmitter and detector unit outside the reactor, this interface physically penetrates the bioreactor bag. These sensors must be reasonably affordable because they are placed alongside the bioreactor. The in-situ sensors must also adhere to the rule that they must not leak any extractable substances into the fermentation medium, even after sterilising. Electrochemical pH sensors, ion selective field effect transistors (ISFETs), chemo- and biosensors for the detection of metabolites such as glucose, glutamine, or lactate, and passive radio frequency identification (RFID) sensing components are a few examples of sensors that fall under this category. Chatterjee et al. offer a technique for measuring O_2 and CO_2 concentrations in bioprocesses using in-situ disposable sensors. They employed an oxygen- and carbon dioxide-permeable in-situ silicone loop. Through gas impermeable tubing, the two gases are recirculated to the corresponding gas sensors outside the SUB. More details on carbon dioxide and oxygen measurements in single-use reactors.

Single-use electrochemical pH sensor

The pH probe is one of the most often used electrochemical sensors for bioprocess monitoring and control. Traditional glass electrodes for potentiometry are well-known, dependable, and durable but are too expensive to discard after just one cultivation run. Glass electrodes that are only used once have been created as a result. These sensors can be built right into the bioreactor during construction and are dry-storable. The sensors comprise a reference electrode and a pH sensor, and they are highly accurate even after radiation. Even some probes come with an integrated temperature sensor for signal temperature correction. The CerCell systems or the ambr® 250 (Sartorius Stedim Biotech, Göttingen, Germany) are two examples of single-use electrochemical pH probes in use (CerCell ApS, Holte, Denmark). Glass electrodes for single use are still highly expensive, hence cost optimization is required.

Conclusion

New sensors are required for bioprocess monitoring in single-use equipment in order to better understand and optimise the process. Although there are many sensor systems available for bioprocess analysis, only a small number have so far been modified for use with disposable reactors. Single-use systems provide new opportunities for applying sensor technologies that are already available but challenging to integrate into traditional bioreactors (e.g., biosensors). Particularly advantageous for transfer to disposable applications are noninvasive setups like spectroscopic or ultrasonic sensors. Future uses of wireless technology, such as RFID chips or free-floating sensor spheres, have a lot of potential because they do not require reactor bag penetration. Although the industry prefers a straightforward conversion of innovative sensors into conventional systems, it should be remembered that new technologies present the possibility of an enhanced or entirely redesigned implementation of sensors. This would make it possible to create brand-new, cutting-edge reactor designs and user interfaces. While researchers must continue to enhance the reliability, repeatability, and robustness of the sensor systems, device and SUB manufacturers must collaborate to create plug-and-play devices and standard interfaces. The industry's readiness to use new technology is crucial to this development.

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