5-7-2017

**XDR-500 MO—Single-use fermentor for microbial processes**

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Xcellerex™ XDR-500 MO single-use fermentor for microbial processes

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Abstract and introduction

Single-use bioreactors are well-established in mammalian cell-based biopharmaceutical productions. However, adoption of single-use technologies for microbial/yeast-based production has been slow due to the unique requirements of fermentation processes. The typical challenges include supporting high-cell density cultivations, high oxygen transfer capacity, and efficient heat removal. Here, we present the single-use XDR-500 MO stirred-tank fermentor system specifically designed for microbial/yeast applications. The performance of the fermentor was evaluated using an E. coli fed-batch process producing a domain antibody (IgM) as a model system. The process was originally developed for a lab-scale conventional stainless steel (SS) system. This work describes the strategy applied to transfer and scale-up this process to the single-use bioreactor (SUB) without the need for extensive re-optimization due to technology change. Moreover, process economy of dAb production based on single-use and conventional technology was compared in silico.

Materials and methods

Fed-batch process for E. coli RV308 clone expressing a dAb, originally developed for lab-scale conventional SS bioreactor, was transferred and scaled up to XDR-500 MO SUB. Fermenter medium complemented with yeast extract in combination with 60% (w/v) glycerol substrate feed was used for cultivations. Process parameters critical for dAb expression were kept constant between technologies, while others were adapted to single-use technology (Table 1). Dissolved oxygen level was controlled by stirrer speed, airflow, and oxygen enrichment of airflow in the single-use system. This work describes the strategy applied to transfer and scale-up this process to the single-use bioreactor (SUB) without the need for extensive re-optimization due to technology change. Moreover, process economy of dAb production based on single-use and conventional technology was compared in silico.

Table 1. Process transfer and scale-up strategy

<table>
<thead>
<tr>
<th>Process parameters</th>
<th>Kpt constant</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH and DO set points</td>
<td>DO control strategy</td>
<td>Medium and feed composition</td>
</tr>
</tbody>
</table>

Critical process parameters like dissolved oxygen level, pH, and temperature were controlled efficiently within their targeted range under the entire cultivations. Temperature was maintained at 37°C ± 0.1°C even when metabolic heat generation peaked at 38 000 BTU/h. Instead of increasing headspace pressure, DO was maintained with oxygen enrichment, enabling cell growth to high cell densities.

Experimental results

Improved process understanding during transition to SUB indicated substrate overfeeding in the SS bioreactor. Evaluation of three reduced feed regimes showed that even applying as low as 60% of the original feed rate to KDR-500 MO was sufficient to maintain cell growth, as shown for XDR Run 1 in Figure 1, and product formation was found to be at comparable levels to the original process. The reduced substrate feed also led to decreased oxygen consumption rates. Levels of expressed dAb achieved in KDR-500 MO after process transfer and scale-up were reproducible and comparable with the SS bioreactor (Fig 2) even without process optimization. Furthermore, it was shown that dAb concentration increased linearly after induction (Fig 5), indicating a straightforward strategy to improve productivity.

Table 2. Comparison of process economy for dAb production between XDR-500 MO SUB and SS bioreactor (Scenario 1 – Single product facility) and (Scenario 2 – Multi product facility)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Scenario 1 – Single product facility</th>
<th>Scenario 2 – Multi product facility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Bioreactor</td>
<td>SS</td>
<td>SS/ SUB</td>
</tr>
<tr>
<td>Maximum number of batches</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Relative cost comparison</td>
<td>1x</td>
<td>1.6x</td>
</tr>
<tr>
<td>Relative facility utilization</td>
<td>1x</td>
<td>1.5x</td>
</tr>
</tbody>
</table>

Conclusions

• XDR-500 MO allowed robust control of challenging process parameters (DO, pH, temperature)
• The model process successfully transferred and scaled up from SS bioreactor to SUB without the need for extensive modifications.
• Cell growth and dAb production level were comparable across technologies/scales even with the implemented changes.
• Higher production flexibility and facility utilization can be achieved with single-use systems.
• Single-use systems are viable alternatives to conventional SS bioreactors for microbial processes.